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ADVANCES IN ADULT AND NON-EMBRYONIC STEM CELL RESEARCH

HEARING

BEFORE THE

SUBCOMMITTEE ON SCIENCE, TECHNOLOGY, AND SPACE

OF THE

COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION
UNITED STATES SENATE

ONE HUNDRED EIGHTH CONGRESS

FIRST SESSION

JUNE 12, 2003

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SENATE COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION

ONE HUNDRED EIGHTH CONGRESS

FIRST SESSION

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ADVANCES IN ADULT AND NON-EMBRYONIC STEM CELL RESEARCH

THURSDAY, JUNE 12, 2003,

U.S. SENATE,
SUBCOMMITTEE ON SCIENCE, TECHNOLOGY, AND SPACE,
COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION,
Washington, DC.

The Subcommittee met, pursuant to notice, at 2:46 p.m. in room SR–253, Russell Senate Office Building, Hon. Sam Brownback, Chairman of the Subcommittee, presiding.

OPENING STATEMENT OF HON. SAM BROWNBACK, U.S. SENATOR FROM KANSAS

Senator BROWNBACK. The hearing will come to order. I want to thank everybody for being here today, particularly the witnesses that traveled some distance. We have a couple of really special ones—not that all of you aren't special, but I think you're going to find these just particularly heartening stories of incredible things that have taken place.

Today, we'll be conducting a hearing on some of the exciting new advances being made in the fields of adult and non-embryonic stem cell research. As I'm sure many of you know, the field of regenerative medicine offers great hope to those suffering from this disease. Much of the research that is providing new hope to those who are currently suffering is moving along at a fast pace and is doing so without questionable or morally controversial techniques.

At this hearing, we will examine some of these advances. This hearing is not about human cloning or destructive human embryonic stem cell research. Rather, it is about some of the other important scientific discoveries that are being made using noncontroversial techniques that rely on adult or non-embryonic stem cells. And these are some processes that only a year-and-a-half ago, we'll recall, were being called "junk science." And yet you're going to hear today from people that have been cured. So there's been amazing work, fabulous work, that has really resulted in people's lives being changed.

In particular today, we will hear from cord-blood stem cell researchers, as well as others, who are working hard in the field of regenerative medicine to find the cures to the diseases that plague humanity. At this hearing, we will discuss not only some of the research that is being conducted, but also some of the treatments that are currently being offered. And we will hear from some of the patients who are benefiting from this important life-saving research. The stories that we will hear from some of the patients will

truly be astounding. They are miraculous. We all agree on the need to work hard toward a cure for the diseases that plague humanity, and we're going to be listening to some of that success here today.

Now, rather than discussing this, I'd like to take advantage of the panels that we have here today to testify. I want to turn to our first panel of people to testify. And they are Dr. David Hess, M.D., Chairman and Professor, Department of Neurology, Medical College of Georgia, in Augusta, Georgia; Dr. Joanne Kurtzberg, M.D., Director of the Pediatric Stem Cell Transplant Program at Duke University Medical Center, in Durham, North Carolina—being a KU grad, I'm familiar with Duke——

[Laughter.]

Senator BROWNBACK.—and a very good school, other than in basketball——

[Laughter.]

Senator BROWNBACK.—Dr. John W. McDonald, M.D., Ph.D., Washington University School of Medicine, Department of Neurology, in St. Louis, Missouri; Dr. Jean Peduzzi-Nelson, Ph.D., University of Alabama at Birmingham; and Dr. Pablo Rubinstein, M.D., Director of Placental Blood Program, New York Blood Center, New York, New York.

I'm delighted to have such a distinguished panel here with us today to testify. I look forward to your testimony. If you would, we will run the clock on 7 minutes. We will take your full testimony into the record. I think it's always best for people to summarize somewhat in putting it forward, so it can save time, as well, for questions afterwards.

We do have an active floor running today. We may have to have recesses periodically, for me to go over and vote. Other members will probably be joining us, as well, so there may be some people stepping in.

[The prepared statement of Senator Brownback follows:]

PREPARED STATEMENT OF HON. SAM BROWNBACK, U.S. SENATOR FROM KANSAS

Thank you for coming to our hearing today.

Today, we will be conducting a hearing on some of the exciting new advances being made in the fields of adult and non-embryonic stem cell research.

As I am sure many of you here know, the field of regenerative medicine offers great hope to those suffering from disease. Much of the research that is providing new hope to those who are currently suffering is moving along at a fast pace and is doing so without questionable or morally controversial techniques.

At this hearing we will examine some of these advances.

This hearing is not about human cloning, or destructive human embryonic stem cell research.

Rather, it is about some of the other important scientific discoveries that are being made using non-controversial techniques that rely on adult or non-embryonic stem cells.

In particular, today we will hear from cord blood stem cell researchers as well as others who are working hard in the field of regenerative medicine to find the cures to the diseases that plague humanity.

At this hearing we will discuss not only some of the research that is being conducted but also some of the treatments that are currently being offered.

And, we will hear from some of the patients who are benefitting from this important life-saving research. The stories that we will hear from some of the patients will truly be astounding.

Regardless of how the members of this committee feel on the controversial issues of human cloning and destructive human embryonic stem cell research, certainly, we can all agree on the need to work hard toward a cure for the diseases that plague humanity.

Now, rather than describe some of the advances being made I would like to turn to our first panel.

Senator BROWNBACK.With that, Dr. Hess, I'd like to invite your testimony, and we will move on down this panel list.

STATEMENT OF DAVID C. HESS, PROFESSOR AND CHAIRMAN, DEPARTMENT OF NEUROLOGY, MEDICAL COLLEGE OF GEORGIA

Dr. HESS. Thank you, Senator Brownback.

I'm David C. Hess. I'm Professor and Chairman of the Department of Neurology at the Medical College of Georgia. I am a physician and neurologist, and that's a specialist that cares for people with neurological diseases.

Many neurological diseases, such as strokes, spinal-cord injury, Alzheimer's disease, Parkinson's disease, and Lou Gehrig's disease, are formidable foes, resistant to treatment, and take an enormous toll in suffering, like you mentioned. A week will not pass when I do not receive an e-mail or a call from a suffering patient asking for a stem cell injection to help them recover their ability to walk or to speak. Some patients are so desperate that they offer up themselves to be the first patient to try the stem cells. I can't blame them. There are few effective treatments for their diseases, and they are looking for any ray of hope.

As you mentioned, Senator Brownback, there is some foundation for their hope. The field of regenerative medicine is taking off, and there are new regenerative-medicine and stem cell institutes and centers being established all over the country.

Many scientific dogma have been slain in the past 5 years. One dogma was that we don't make new brain cells in our brain, in adults. In other words, you steadily lose what you have. However, in a set of clever experiments, it has recently been shown that humans, even in their 60s and 70s, can make new nerve cells in their hippocampus, a comforting fact for all of us.

Adult stem cells can be obtained from a variety of organs, ranging from the brain's so-called neural stem cells to the skin. However, the best study is that most accessible adult stem cells are in the bone marrow. Bone marrow is a rich source of stem and progenitor cells. I will briefly review the potential of adult stem cells derived from the bone marrow.

As a physician, my motivation is to see some of these cells used to treat these devastating neurological diseases that I see every day. And as a physician researcher, I'm trying to make some small contribution to the stroke-recovery field, thanks to past support from the American Heart Association and, presently, the NIH.

Let me explain. Bone marrow contains two major types of stem or progenitor cells, and maybe many more. The two major types are the hematopoietic stem cells and the mesenchymal stem cells, or what are often called marrow stromal cells.

Hematopoietic stem cells have been used for years in bone-marrow transplants and have cured thousands of patients with leukemias and other forms of cancer. These hematopoietic stem cells have the ability to circulate throughout the whole body and reach every organ in the body. Their plasticity—that is, their ability to turn into other cell types of cells, such as nerve cells, liver cells,

and pancreas cells that produce insulin—is still hotly debated; however, there is evidence that these cells can turn into Purkinje cells in the brain, a very sophisticated type of nerve cell. And this phenomena is not just restricted to rodents. There is now autopsy evidence from humans that bone-marrow cells can form new neurons in the brain. There may also be other bone-marrow-derived cells that circulate in the peripheral blood, with stem cell or progenitor cell qualities.

Recently, the progeny, or the daughter, of the hematopoietic stem cell, so to speak, circulating blood monocytes, have been shown to be able to differentiate into nerve cells and blood-vessel cells called endothelial cells. This is potentially of great clinical relevance, as monocytes are easy to isolate from human blood and could be a rich source of replacement cells.

There are also bone-marrow cells that do not normally circulate in the bloodstream, but, instead, reside in the bone marrow and service supporting cells for the hematopoietic stem cells. These cells are called mesenchymal stem cells, or marrow stromal cells. It is these cells that are the source of much excitement in the field of regenerative medicine.

Some of the most exciting research, in terms of an eventual human clinical application, are the multipotent adult progenitor cells isolated by Catherine Verfaillie. These can be isolated from both rodent and human bone marrow. They are able to turn into cells of all three germ layers. That is, they can turn into endothelial cells, which line the blood vessels, liver cells, and nerve cells. And, importantly, they don't just do this in a petri dish; they are also able to do it in the live animal. Moreover, they do not die prematurely, and, importantly, they do not form teratomas, or tumors, like embryonic stem cells tend to do.

Dr. Walter Low, a collaborator of Dr. Verfaillie, has recently shown that these MAPCs can aid in brain repair after stroke in a rodent. The obvious advantage of these cells for regenerative medicine is that they can be easily isolated from human bone marrow and the potential for a patient to be cured or treated with their own cells, without any fear of rejection.

A closely related cell type is the marrow stromal cell. Marrow stromal cells have been shown to be involved in brain repair after stroke and traumatic brain injury, by Dr. Michael Chopp, at Henry Ford Hospital, and to repair the injured spinal cord, by Dr. Darwin Prockop's group at Tulane. Like many other adult stem cells, these cells can be delivered intravenously, and they can home to the injured tissue, almost like a guided missile. There appear to be chemical signals released by injured tissue that attract these cells. Marrow stromal cells are easy to culture, easy to expand; and, since they can be autologous, they would not be rejected.

How, exactly, these cells repair injured tissue is not clear. While, in some cases, there is actual replacement of injured cells, it seems more likely that these cells serve as growth-factor factories and aid the tissue to repair itself.

There's also another type of circulating bone-marrow-derived cell, the so-called endothelial progenitor cell that has attracted much recent interest. EPCs circulate in the bloodstream and form new endothelial cells in blood vessels. We now know that these EPCs con-

tribute to organ repair after cutting off blood supply to the heart, the limbs, and the brain. This is critically important, as cardiovascular disease and stroke are two of the three biggest killers in the United States. We have learned that by giving animals extra doses of these EPCs, we can improve their outcome from heart attack and salvage their limbs that are starved for blood.

The field is moving very, very fast. Bone-marrow-derived cells are already being tested in small numbers of patients with heart attacks. The TOPCARE trial was a trial published in the journal, The Lancet. And, in this, bone-marrow cells, harvested from the patient's own bone marrow or their blood, were delivered via a catheter in the coronary artery to these patients. The procedure was safe, and the initial results were encouraging, though this was a very small trial.

Another type of bone-marrow blood stem cell, which you're going to hear about later, is the human umbilical cord stem cell. These are derived from umbilical cords that are normally discarded after a delivery. Umbilical cord blood is a rich source of stem cells. These have already been exploited as a source of bone-marrow transplants in the cancer field and in sickle-cell anemia.

These umbilical cord stem cells also have great potential as a treatment for neurological disease. When delivered intravenously to a rodent with a stroke, they help improve the outcome of that stroke in that rodent.

Despite these hopeful signs, much work needs to be done. Before we are able to treat humans safely and effectively, we need to define the optimal dosing of these cells, the optimal type of bone-marrow populations to use, and the timing of when to administer them. And then how should we administer them? Should we give them directly into the tissue, like into the heart or the brain? Should we deliver them intravenously, or should we give them in an artery? There's multiple avenues that we could give them. We also need to learn more about how these bone-marrow cells and other adult stem cells home or go to the damaged tissue.

The major advantages of bone-marrow-derived stem cells are that they are autologous, with the exception of umbilical cord stem cells, and, therefore, they are less likely to be rejected. They can be easily isolated from bone-marrow aspirates, which are done clinically, and they avoid the ethical concerns that many have with embryonic stem cells.

However, we have to keep in mind that repairing the central nervous system is a daunting task. Neurons make tens of thousands of connections with other nerve cells. Some of them send projections, or axons, from meters—feet, literally—and it's very important that they connect up to the other cell.

In most of the experiments, so far, we have little evidence that any stem cell delivered into an adult will be able to make all these connections and become fully functional. It is likely that most of the cell transplants in the brain work by stimulating the brain to actually repair itself. We need to learn more about enhancing these self-repair processes.

In the growing field of cell therapy, we will need to target diseases with specific cell types and approaches. One size will not fit all. We may need to treat some of these diseases with a combina-

tion of both cells and different growth factors. The treatments we develop for Parkinson's disease will probably be vastly different from those we develop for stroke. There are no magic bullets; only painstaking research and more funding will allow us to advance.

Thank you.

[The prepared statement of Dr. Hess follows:]

PREPARED STATEMENT OF DAVID C. HESS, PROFESSOR AND CHAIRMAN, DEPARTMENT OF NEUROLOGY, MEDICAL COLLEGE OF GEORGIA

I am David C. Hess M.D., Professor and Chairman of the Department of Neurology at the Medical College of Georgia. I am a physician and neurologist, a specialist that cares for people with neurological diseases. Many neurological diseases such as stroke, spinal cord injury, Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis (Lou Gehrig's disease) are formidable foes, resistant to treatment and take an enormous toll in suffering. A week will not pass when I do not receive an e-mail or a call from a suffering patient asking for a stem cell injection to help them recover their ability to walk or speak.. Some patients are so desperate that they offer up themselves to be the first patient to try the stem cells. I can't blame them; there are few effective treatment for their diseases and they are looking for any ray of hope. They have also been influenced by exaggerations in the media.

Yet there is some foundation to their hope. The field of "regenerative medicine" is taking off and there are new "Regenerative Medicine" and "Stem Cell" institutes and centers being established all over the country. Many scientific dogma have been slain in the past 5 years. One dogma was that new neurons are not born in the brains of humans-in other words, you just steadily lose what you have as you age. However, in a set of clever experiments by Drs. Ericksson and Gage in1998 it was shown that humans even in their 60s can make new nerve cells in their hippocampus, a comforting fact for all of us. Moreover, mice make more new neurons if they are kept in an "enriched" environment and exercise (Kempermann, 2002). If we can extrapolate these findings to humans, it suggests that by keeping our minds active we are less likely to lose them. We also now know that new neurons can be made in response to a brain injury in other parts of the rodent brain, not just the hippocampus. For example, after a stroke, new neurons are born and travel to the damaged tissue and appear to aid in its repair (Arvidsson, 2002). Now we have to learn how to enhance and stimulate these natural repair mechanisms.

Adult stem cells can be obtained from a variety of organs ranging from the brain (so called neural stem cells) to the skin. However, the best studied and most accessible adult stem cells are in the bone marrow. Bone marrow is a rich source of stem and progenitor cells. I will briefly review the potential of adult or non-embryonic stem cells to treat human disease. I will focus on bone marrow stem cells. As a physician my perspective is on the clinical potential of these advances and my motivation is to see some of these cells used to treat these devastating neurological diseases that I see every day. As a physician-researcher, I am trying to make some small contributions to the stroke recovery field thanks to past support from the American Heart Association and currently the NIH.

Bone marrow contains two major types of stem or progenitor cells and maybe many more. The two major types are the hematopoietic stem cells and the mesenchymal stem cells or marrow stromal cells. Hematopoieitc stem cells have been used for years in bone marrow transplants and have cured thousands of patients with leukemias and other forms of cancer. These hematopoietic stem cells and their progeny-the white blood cells, red blood cells and platelets-have the ability to circulate throughout the bloodstream and reach every organ in the body. Their plasticity, that is, the ability of these cells to "turn "into other cell types such as nerve cells, liver cells and pancreas cells that produce insulin, is still hotly debated. However, there is evidence that these cells can rarely differentiate into Purkinje cells in the brain, a very sophisticated type of neuron. The phenomenon is not restricted to rodents; there is now autopsy evidence from humans that bone marrow cells are involved in the formation of neurons at a low level (Mezey, 2003)

Some recent evidence had suggested that cell fusion was responsible for some of the plasticity that had been described for bone marrow stem cells (Terada, 2002; Wang, 2003; Vassilopoulos, 2003). In cell fusion, the bone marrow cells would not actually "turn into" another cell type-they would just fuse with the mature cell giving it twice the number of chromosomes and thereby making it potentially unstable. However, while cell fusion may indeed account for some of the "plasticity" of bone

marrow cells, particularly in the liver, it does not seem to account for all of it. In recent work, bone marrow cells have been shown to become functional insulin-secreting cells in the pancreas of mice without any evidence of cell fusion (Ianus, 2003).

There may also be bone marrow-derived cells that circulate in the peripheral blood with "stem cell" or "progenitor cell" qualities. Recently the progeny of the hematopoietic stem cell, a subpopulation of circulating blood monocytes, have been shown to be able to differentiate into nerve cells and blood vessel cells called endothelial cells (Zhao, 2003). This is potentially of great clinical relevance as monocytes are easy to isolate from human blood and could be a rich source of replacement cells.

There are also bone marrow cells that do not normally circulate in the bloodstream but instead reside in the bone marrow and serve as supporting cells for the hematopoietic stem cells. These cells are called mesenchymal stem cells or marrow stromal cells. It is these cells that are the source of much excitement in the field of regenerative medicine. Some of the most exciting research, in terms of an eventual human clinical application, are the Multipotent adult progenitor cells (MAPC) isolated by Catherine Verfailie and described comprehensively in the July 2002 issue of Nature (Jiang, 2002). These cells can be isolated from rodent and human bone marrow. They are able to differentiate into cells of all three germ layers (endoderm, mesoderm and ectoderm) that is they can from endothelial cells or blood vessel lining cells, hepatocytes (liver cells), and nerve cells. They not only do this in the petri dish, they also do it in the live animal. Moreover, they do not senesce or die prematurely and importantly they do not form teratomas or tumors like embryonic stem cells tend to do. Dr. Walter Low a collaborater of Dr. Verfaillie has shown that these MAPCS can aid in brain repair after stroke in a rodent (Zhao, 2002). The obvious advantages of these cells for regenerative medicine is their easy isolation from human bone marrow and the potential for a patient to be their own donor without fear of rejection.

A closely related cell type is the marrow stromal cell. Marrow stromal cells have been shown to be involved in brain repair after stroke and traumatic brain injury by Dr. Chopp at Henry Ford Hospital and to repair the injured spinal by Dr. Darwin Prockop's group at Tulane. Like many other adult stem cells, these cells can be delivered intravenously and then "home" like a guided missile to the injured tissue. There are chemical signals released by injured tissue that attract these cells. Marrow stromal cells are easy to culture, easy to expand, and since they are autologous they would not be rejected. How exactly these cells repair injured tissue is not clear. While in some cases this is actual replacement of damaged cells, it seems more likely that these cells serve as growth factor "factories" and aid the tissue to repair itself by reactivating latent developmental programs.

There is also another type of circulating bone marrow-derived cell, the endothelial progenitor cell (EPC) that has also attracted much recent interest. Endothelial cells are cells that line all the blood vessels of the body. Besides being mere conduits for blood, we now know that they play an active and necessary role in the development and sustenance of the body's organs. Bone marrow cells that can circulate in the bloodstream and form new endothelial cells and blood vessels were first described and characterized in 1997 (Asahara). We now know that these EPCS contribute to vessel and organ repair after ischemia to the heart, limbs and brain (Rafii, 2003). This is critically important as cardiovascular disease and stroke are two of the three biggest killers in the U.S. We have learned that by giving animials extra doses of these EPCS, we can improve their outcome from heart attack and salvage their limbs that are starved for blood.. Also, these EPCs can be mobllized from the bone marrow and into the peripheral blood with drugs and different growth factors . Some of these growths such G–CSF are already approved by the FDA for other indications

The field is moving fast. Bone marrow-derived stem cells are already being tested in small numbers of patients with heart attacks. In the TOPCARE trial, bone marrow cells harvested from the same patient's bone marrow or their blood were delivered via a catheter in the coronary artery to injured heart tissue (Assmus, 2002). The procedure was safe and initial results were encouraging. There is also a trial using bone marrow cells in patients with congestive heart failure (Perin, 2003).

Another type of bone marrow or blood stem cell is the human umbilical cord stem cell. These are derived from umbilical cords that are normally discarded after a delivery. Umbilical cord blood is a rich source of stem cells. These have already been exploited as a source of bone marrow transplants in the cancer field. These umbilical cord stem cells also have great potential as a treatment for neurological diseases. When delivered intravenously to a rodent with a stroke, they help improve the recovery from the stroke (Chen, 2001).

Despite these hopeful signs, much work needs to be done. Before we are able to treat humans safely and effectively, we need to define the optimal dosing of these cells, the optimal type of bone marrow populations to use, the timing of when to administer, and the best route of administration (inject directly into the organ, intravenously, intra-arterially). We also need to learn more about how they these bone marrow cells and other adult stem cells home to damaged tissue so we can exploit this therapeutically.

The major advantages of bone marrow derived stem cells are: 1) they are autologous (except for umbilical cord stem cells) and will not be rejected; 2) they can be easily isolated from bone marrow aspirates; and 3) they avoid the ethical concerns that many have with embryonic stem cells. However, we also have to keep in mind that repairing the nervous system is a daunting task. Neurons make tens of thousands of connections with other neurons. Some send their projections (axons) for meters and then connect to another cell. In most of the experiments so far we have little evidence that stem cells delivered into an adult will be able to make all these connections and become fully functional. It is likely that most of the cell transplants in the brain work by stimulating the brain to repair itself. We need to learn more about enhancing these endogenous (self) repair processes. In this growing field of "Cell Therapy", we will need to target diseases with specific cell types and approaches-one size will not fit all. We may need to treat some of these diseases with a combination of both "cells" and growth factors. The treatments we develop for Parkinson's disease will be different from those we develop for stroke. There are no magic bullets-only painstaking research will allow us to advance.

References

Arvidsson A., Collin T., Kirik D., Kokaia Z., Lindvall O. Neuronal replacement from endogenous precursors in the adult brain after stroke. Nat Med. 2002 Sep; 8(9):963–70.

Asahara T., Murohara T., Sullivan A., Silver M., van der Zee R., Li T., Witzenbichler B., Schatteman G., Isner J.M. Isolation of putative progenitor endothelial cells for angiogenesis. Science. 1997 Feb 14; 275(5302):964–7. Assmus B., Schachinger V., Teupe C., Britten M., Lehmann R., Dobert N., Grunwald F., Aicher A., Urbich C., Martin H., Hoelzer D., Dimmeler S., Zeiher A.M.; Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction.Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE–AMI). Circulation. 2002 Dec 10; 106(24):3009–17.

Chen J., Zhang Z.G., Li Y., Wang L., Xu Y.X., Gautam S.C., Lu M., Zhu Z., Chopp M. Intravenous administration of human bone marrow stromal cells induces angiogenesis in the ischemic boundary zone after stroke in rats. Circ Res. 2003 Apr 4; 92(6):692–9

Chen J., Sanberg P.R., Li Y., Wang L., Lu M., Willing A.E., Sanchez-Ramos J., Chopp M.Intravenous administration of human umbilical cord blood reduces behavioral deficits after stroke in rats. Stroke. 2001 Nov; 32(11):2682–8.

Eriksson P.S., Perfilieva E., Bjork-Eriksson T., Alborn A.M., Nordborg C., Peterson D.A., Gage F.H.. Neurogenesis in the adult human hippocampus. Nat Med. 1998 Nov; 4(11):1313–7

Hofstetter C.P., Schwarz E.J., Hess D., Widenfalk J., El Manira A., Prockop D.J., Olson L. Marrow stromal cells form guiding strands in the injured spinal cord and promote recovery. Proc Natl Acad Sci USA. 2002 Feb 19; 99(4):2199–204.

Ianus A., Holz G.G., Theise N.D., Hussain M.A.. In vivo derivation of glucose-competent pancreatic endocrine cells from bone marrow without evidence of cell fusion. J Clin Inest 2003 March 111(6): 843–50

Jiang Y., Jahagirdar B.N., Reinhardt R.L., Schwartz R.E., Keene C.D., Ortiz-Gonzalez X.R., Reyes M., Lenvik T., Lund T., Blackstad M., Du J., Aldrich S., Lisberg A., Low W.C., Largaespada D.A., Verfaillie C.M. Pluripotency of mesenchymal stem cells derived from adult marrow.. Nature 2002 Jul 4; 418(6893):41–9

Kempermann G., Gast D., Gage F.H. Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. Ann Neurol. 2002 Aug; 52(2):135–43.

Li Y., Chen J., Chen X.G., Wang L., Gautam S.C., Xu Y.X., Katakowski M., Zhang L.J., Lu M., Janakiraman N., Chopp M.. Human marrow stromal cell therapy for stroke in rat: neurotrophins and functional recovery. Neurology. 2002 Aug 27; 59(4):514–23 Mezey E., Key S., Vogelsang G., Szalayova I., Lange G.D., Crain B. Transplanted bone marrow generates new neurons in human brains. Proc Natl Acad Sci USA. 2003 Feb 4; 100(3):1364–9 Perin E.C., Geng Y.J., Willerson J.T. Adult stem cell therapy in perspective. Circulation. 2003 Feb 25; 107(7):935–8.

Rafii S., Lyden D. Therapeutic stem and progenitor cell transplantation for organ vascularization and regeneration. Nat Med. 2003 Jun; 9(6):702–12.

Terada N., Hamazaki T., Oka M., Hoki M., Mastalerz D.M., Nakano Y., Meyer E.M., Morel L., Petersen B.E., Scott E.W.. Bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion. Nature. 2002 Apr 4; 416(6880):542–5 Vassilopoulos G., Wang P.R., Russell D.W.. Transplanted bone marrow regenerates liver by cell fusion. Nature. 2003 Apr 24; 422(6934):901–4 Wang X., Willenbring H., Akkari Y., Torimaru Y., Foster M., Al-Dhalimy M., Lagasse E., Finegold M., Olson S., Grompe M.. Cell fusion is the principal source of bone-marrow-derived hepatocytes. Nature. 2003 Apr 24; 422(6934):897–901

Zhao L.R., Duan W.M., Reyes M., Keene C.D., Verfaillie C.M., Low W.C.. Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats. Exp Neurol. 2002 Mar; 174(1):11–20. Zhao Y., Glesne D., Huberman E. A human peripheral blood monocyte-derived subset acts as pluripotent stem cells. Proc Natl Acad Sci USA 2003 Mar 4; 100(5):2426–31

Senator BROWNBACK. What you're describing is exciting and I hope this is a field that we can put much additional research funding into.

Dr. Rubinstein, thank you very much for joining us today.

STATEMENT OF PABLO RUBINSTEIN, M.D., DIRECTOR OF PLACENTAL BLOOD PROGRAM, NEW YORK BLOOD CENTER

Dr. RUBINSTEIN. Thank you very much, Senator. We are grateful for the opportunity to address this Committee.

The work I will describe refers to the stem cells that are present in cord blood. This work, which will be presented by both myself and Dr. Kurtzberg, has taken place over a number of years, as I will describe.

The first evidence that there were stem cells in cord blood was reported in 1974. From that time to the present, the most important elements in this history are the first cord-blood transplant that occurred in 1988. During the intervening years, there was a lot of research done that allowed this to happen. From 1988, where the first patient was transplanted by—a patient from Duke University, a patient of Dr. Kurtzberg's.

The next big element was the setting up of a cord-blood program for treating patients without sibling donors, where we collect cord blood from unrelated donors, with informed consent, and this blood is frozen and then is available for use on anyone who needs them. The first unrelated cord-blood transplant from our repository at New York Blood Center was performed by Dr. Kurtzberg at Duke in 1993.

And the next step in this story is the exemption granted by the FDA for us to continue this research and to expand the range of documented indices of the activities of these transplants. This year, there have been more than 3,500 transplants performed worldwide, so far, with cord blood. Of these, more than 2,000 have been in the United States, and 1,370 from our own cord-blood bank.

The NIH has recognized the importance of this work and has created a second study, the COBLT study, which Dr. Kurtzberg participated, both of the transplanted and as a banker, to produce more of these transplants for patients in need. Dr. Kurtzberg will also report beautiful results that have been obtained with patients with cord-blood transplants that repaired, or at least helped to repair, tissues other than the blood and the immune system, which are a direct province of the stem cells in the cord blood.

How is cord blood prepared and used? After the birth of a healthy baby, the placenta is removed, with the major segment of the cord, and the baby goes one way; the placenta is taken out. Normally, this placenta, with the segment of the cord, is discarded. In our case, we drain the blood that is left in the placenta, and we take it to the laboratory, process it, freeze it down, and, as the slide shows, we have special containers that allow us to freeze it in liquid nitrogen. At the temperature of liquid nitrogen, this blood will be available for transplantation for many years, without attrition. The blood is stored in special containers, which maintain control and information, directly in the same device.

Results that have been obtained in the clinical use of this cord blood over the years allow us to compile a list of advantages that cord blood offers to clinicians and patients, in comparison with bone marrow. There are, first of all, no risks to the donors. There is no donor attrition. The blood will stay frozen until it's used. If it is processed correctly, it will be available for many years. We don't know how many, because it's longer than has been used, so far over 15 years. Grafts are available on short notice. They can be produced, and routinely are produced, in our case, within days, not months or years. There are fewer latent viral infections in cord blood than in adult bone marrow.

But the main reason why this blood is so important is because the immune reaction that the donor's cells exert against the recipient's tissues, which is a problem with bone-marrow transplantation, is much weaker in the case of cord blood; probably reflecting the biological status of that blood that comes from an organism in which the mother and the child have to tolerate each other. This advantage allows us to perform transplants with some mismatches. In bone-marrow transplantation, the more mismatches, the more problems occur for the patient; not just immediate, but for a long time for those patients who are successfully treated.

That allows us, therefore, to find matches for people who have very much difficulty finding matches, people with rare types and people of ethnic minorities in which the opportunities to find a donor among those in the volunteer donor groups is much less, simply because there are fewer of them in the population.

Another important result, which is now being shown in the slide, has been obtained in cooperation with the International Bone Marrow Transplant Registry. Several hundred patients transplanted with bone marrow were compared with cord-blood recipients for the same disease and the same age groups. The cord blood with no more than one mismatch, and the bone marrow with no more than one mismatch, as you can see offer exactly the same long-term transplant survival. What you're not seeing here is that the clinical condition of the patients is different. The cord-blood recipients usually have a much easier time, with much fewer chronic graft versus host disease than the bone marrow.

Another thing the slide doesn't show is that the average result for all types of transplants that are taking place. And in the case cord blood, there is an additional influence. In addition to the matching is the cell dose. You can see, in the panel on the left, that people transplanted with small cell doses have a lower probability of long-term survival. But if we can eliminate, from our transplan-

tation, the need to use those small cord bloods, we can shift the whole curve up and offer an overall larger probability of success.

To terminate, I would just like to show you two slides, which refer to the need. It has been reported by the GAO, in October last year, the situation with bone-marrow transplantation that reflects the fact that in this country, at the moment, for people who need unrelated transplants, the opportunity to get the transplant is estimated at about 9 percent of the total. For the period 1997 to 2000, of an estimated 44,000 patients who needed transplant, 4,056 got them—10 percent of the need, and about a quarter of all of those patients that went all the way to search officially.

Finally, the other aspect of cord blood is, because of its tolerance of mismatches, it's possible to transplant patients of the different minority populations in our country with appropriate transplants. And, in this slide, you can see four populations—Asians, African Americans, Hispanic, and Caucasians. The African American is highlighted as an example. You will see, in the first part of the slide, that the proportion of African Americans, among all those who search, is about 12 percent, which reflects very closely with the size of the African American community in the national scope. However, the donors that were transplanted with bone-marrow transplants by the NMDP is only 6 percent, so only half as much chance as is available if they were equally—if they have equal access to the transplants. With cord blood, however, the probability is 19 percent. And the reason for that is twofold. One is that we can make transplants that are less well matched. And, second, that we can select our donors by harvesting the cord blood in places where we can collect effectively, cord blood from members of these ethnic, and all the ethnic, groups. And, as a result, we can improve the access of these patients to transplantation.

This is my part of the presentation. And now Dr. Kurtzberg will continue.

Senator BROWNBACK. Thank you very much, Dr. Rubinstein.

And, Dr. Kurtzberg, I look forward to your testimony here today.

STATEMENT OF JOANNE KURTZBERG, M.D., DIRECTOR, PEDIATRIC STEM CELL TRANSPLANT PROGRAM, DUKE UNIVERSITY MEDICAL CENTER

Dr. KURTZBERG. We're going to have a little technical switch here.

Senator BROWNBACK. All right.

Dr. KURTZBERG. OK.

Well, thank you very much for listening to our story today about cord blood. I'm going to continue by talking about the clinical applications of cord-blood transplantation, today and in the future.

We've been very excited about cord-blood transplantation, because, as a transplant physician, I, and all others, are faced with patients who need the therapy and don't have donors. And cord blood has filled the niche for those patients, because it can be used without complete matching.

Now, the child shown in this slide was the first recipient ever of a cord-blood transplant. He's from Salisbury, North Carolina, and was transplanted in 1988 with cord blood from his baby sister. And his transplant was extremely important, because there was no way

to really demonstrate or prove, in animal model or in a test tube, that cord blood contains sufficient numbers of stem cells to reconstitute a patient. And there were many skeptics, and most people believed it wouldn't work. But this family was very courageous and allows his baby sister's cord blood to be used for his transplant for a rare genetic diseased, called Fanconi anemia. And he's shown——

Senator BROWNBACK. What was the disease?

Dr. KURTZBERG. Fanconi anemia, which is an inherited disease that causes death in the first decade of life. It's a defect in DNA repair. And it affects all cells in the body; but first, the blood. And it leads to bone-marrow failure, or leukemia, causing death in the first decade of life.

Senator BROWNBACK. Thank you.

Dr. KURTZBERG. This boy was successfully transplanted, successfully engrafted, is shown 15 years later, in the right-hand panel, and is doing well; well, has a durable graft. Again, one of the questions a transplanter would have is, "Will the cells not only grow back at the beginning, but will they stay there, and will they remain and grow with the patient who received them?" And he is the longest living survivor of a cord-blood transplant, the first recipient of a cord-blood transplant. And, at least at 15 years, we can say that this is a durable graft, without causing any late problems.

Now, after his transplant, there were other related transplants performed in small numbers over the next 5 years, but the real breakthrough in cord-blood transplantation came when Dr. Rubinstein's bank was established and there was a pool of donors in the unrelated setting. And it's now been shown that cord blood can be used for all the applications of bone marrow and that includes those listed in the slide—hematologic malignancies, immune deficiencies, like the "bubble boy" disease, marrow-failure syndromes, hemoglobinopathies. And you'll hear from a sickle-cell anemia patient later, who has had his disease corrected with a cord-blood transplant.

And then a very interesting category of diseases called the "inborn errors of metabolism," where babies are born missing enzymes that are necessary for development of the brain or the muscles or the heart or the skeletal system; and where, without therapy, they generally die in infancy or early childhood.

Now, I only have time to show you a little bit of data from patients transplanted with cord blood; and I chose the genetic diseases to focus on, because I think they really illustrate lessons that we can learn to move into the field of regenerative medicine.

This slide shows our results transplanting children with genetic immunodeficiency syndromes—where their immune system is absent at birth. And there are multiple forms of this disease. It's fatal in childhood, without treatment, either because of infection or cancer. And transplant is the only therapy that's curative.

This little boy was transplanted at 18 months of age, when he was critically ill with a fungal infection, and really no one thought he would even make it through the transplant. And he's shown 3 years after transplant, successfully corrected with a normal immune system.

Overall, in about 30 patients with this disease, we have an 80 percent event-free survival, which is shown in that curve. And

what that means is these children are alive, well, engrafted, and they have a recovered immune system that functions normally.

Senator BROWNBACK. And the children would have all died.

Dr. KURTZBERG. They would have all died, yes. These are lethal genetic conditions.

Another example is an inborn error called Hurler syndrome, where children are born missing an enzyme that's necessary for development of the brain, the liver, the bones, the cornea, and the cartilage. And this little girl is an example of a child transplanted with Hurler in infancy. These children generally die by the age of five to 10 years. And although they have severe mental retardation, they actually die of atherosclerotic heart disease because of deposits that fill up the coronary arteries and cause damage to the heart muscle. And transplant, again, will correct this disease. And, in our hands, transplanting now over 25 children, the event-free survival is 90 percent. That means these children are engrafted, corrected. And I just showed you one example of a child transplanted at 5 months of age, now 6 years old, with a normal IQ—actually, a high IQ—and she's a reflection, not an exception. All the children we've treated have had normal development and regained skills that they had lost.

Senator BROWNBACK. And normal IQ development.

Dr. KURTZBERG. Yes, they are in the normal range.

We also know that their bones have corrected, and that they have not developed coronary artery disease, which probably has implications for adult coronary artery disease, although the pathogenesis is different.

A third disease that really falls into a category called leukodystrophy, where there's, again, children born with defects in myelination. Myelin is the covering of the nerve sheath in the white matter of the brain. And without that covering, the brain neurons are damaged and die. Krabbe disease is the most severe leukodystrophy, with the earliest onset, and children who have this disease generally develop normally for the first few months of life and then regress and are vegetative by a year of age, and die between one and two years of age.

Now, the little boy in the picture lost a sibling to Krabbe disease, and the sibling died at 13 months of age. He's shown at 2 years of age, but he was transplanted at 3 weeks of age, because we knew, the cause of his sibling's death we know to look for the disease. And when he was diagnosed, we were able to mobilize a cord blood within a few days. We tested that cord blood to make sure that cord blood didn't carry the disease, and then go forward with a transplant in the first month of life. There have now been ten children treated in the United States with that same approach, and all ten are doing very well anywhere from one to 6 years later.

The survival curves that are portrayed on the graph show you that the newborn transplants, which is the top of the line and is straight, at 100 percent, all are surviving, doing well, and developing normally. Children in the middle line, that goes down and evens out at about 40 percent, are children who had no family history. There was no way to know to look for the disease. They were diagnosed after they had symptoms, and they had some brain damage at that point. And those children have a 40 percent event-free

survival, and they are left with some disability, sometimes severe and sometimes mild.

Senator BROWNBACK. So the age that you catch this is very significant.

Dr. KURTZBERG. Well, it's either the age or the amount of damage or both, and it's hard to know.

And then the other line, that goes all the way down to zero, shows you the natural history of the disease in untreated children. In this case, there are 156 in the curve. And these are children whose families contacted us, and we evaluated, but we felt were too advanced with the disease for the procedure, and so they were not treated, and the disease ran its natural course.

Now, this is an MRI picture. Now, I know it's a little complicated, but it shows the brain of a different child, who was also transplanted, with Krabbe, in the first 3 weeks of life. And what's interesting here is, this is her scan—moving into it with my arrow—at 1 year of age, the smaller brain; and then, on the left-hand panel, 2 years of age. And at 1 year of age, she has some fluffy stuff around the ventricles, which is inflammation, which is abnormal. But, at 2 years of age, that has regressed and has gone away. And, in addition, these gray lines show myelination, which is normal for age. Now, this child would not have been able to myelinate her brain if she had not been transplanted. And, in fact, she probably would not have survived to this age. But this shows actual repair on a scan in a child who is doing well.

This last slide of this Krabbe story shows brain tissue from a child who died. The child was a girl, and she received a transplant from a boy. And these are nuclei of brain cells in the white matter and in something called the choroid plexus, which are the cells lining the ventricles. All the cells that have blue or green dots are male cells, donor cells, that have traveled to this child's brain and distributed throughout the brain. In fact, we found that 30 to 40 percent of the cells in her brain came from the donor, and we're investigating what kinds of cells they are.

But, again, as you think of repairing neurologic damage, this is a hint that maybe these cells have the capacity to do that, and they certainly need to be examined further.

Finally, I want to just end with a few comments about sickle-cell anemia and hemoglobinopathies. Sickle-cell anemia, as you'll hear later, can be cured by hematopoietic stem cell transplantation, either from bone marrow or from cord blood. But many patients don't have donors. And we have transplanted a few patients with sickle-cell disease and leukemia, and cured both diseases.

The little boy in the picture here is a surgeon's son, who has thalassemia, which is another kind of hemoglobinopathy, and he was the first recipient of a cord-blood transplant for hemoglobinopathy, at two-and-a-half months of age, before the disease had caused any damage to any of his organs. And he is going well, at 5 years of age, without any symptoms or problems from the disease.

Personally, I believe that we should be taking the same approach for sickle cell, using the transplant very early in childhood or infancy, where the transplant survival rates are better. This graph shows you event-free survival after related cord-blood transplants,

and they are 90 percent survival, and 80 percent of event-free survival in thalassemia and sickle-cell disease, respectively. And so this works and is better than much of the morbidity that much of the patients who suffer with this disease later will experience.

Also, cord blood has a role here for African American patients, who otherwise can't find donors very quickly.

Cord blood has a lot of applications right now, in the diseases I mentioned and others. It also has applications, I think, in the future for cellular therapies, along with other stem cell sources. And our real request here is to continue to be able to bank cord blood in the public setting.

And very briefly, Dr. Rubinstein told you the history, but the NHLBI had funded both his first public cord-blood bank, and then a second group of banks, under a program called COBLT. Those banks and Dr. Rubinstein's bank have proven that this is an important resource. But now there's no continued funding to take this resource, where really about $20 million was already expended to build it up and continue it. It needs to transfer over to the service sector and be supported through federal dollars.

So our proposal is to establish a national cord-blood program, which will provide grafts for patients in need now and provide an inventory of cells for research and future cellular therapies, and we need to have funding to create a network of four to six banks in the United States that will network together to build an inventory of about 100 to 150,000 units, which are the numbers needed to solve the problems that Dr. Rubinstein illustrated with cell dose and matching.

I'll stop there. Thank you.

[The prepared statement of Dr. Rubinstein and Dr. Kurtzberg follow:]

CORD BLOOD

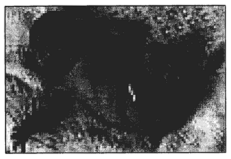
A SOURCE OF STEM AND PROGENITOR CELLS FOR PATIENTS IN NEED OFBONE MARROW TRANSPLANTATION AND OTHER CELLULAR THERAPIES

Pablo Rubinstein, M.D., New York Blood Center and Joanne Kurtzberg, M.D., Duke University

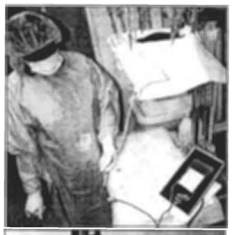
CORD BLOOD RESEARCH PROGRESS

- 1974: First Report on Stem/Progenitor Cells in Human Cord Blood
- 1988: First Cord Blood Transplant (*Sibling*)
- 1992: First Public Cord Blood Bank (*Unrelated Donors. NIH-sponsored Research*)
- 1993: First Unrelated Cord Blood Transplant
- 1996: First FDA IND + NIH Sponsored COBL T Study
- 2003: More than 3500 Cord Blood Transplants Worldwide, 2000 in U.S.
- 2003: Donor-type Cells of Non-Blood or Immune Lineages and Evidence of Myelin Regeneration in Patients with lysosomal storage diseases after Cord Blood Transplant

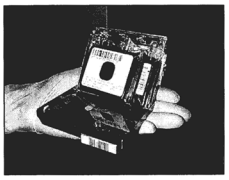
Collection, processing and archiving cord blood for stem cell transplantation by most public cord blood banks



1. After birth, cut cord and separate placenta



2. Collect cord blood by gravity from umbilical cord



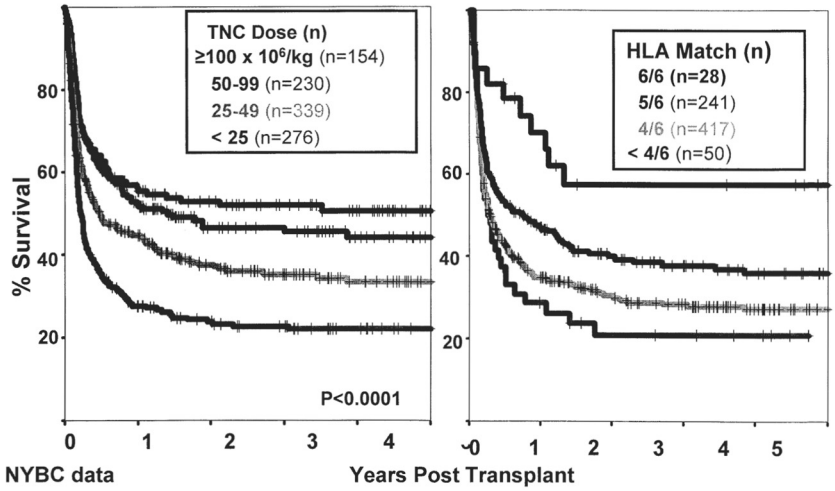
3. Unit of concentrated stem cells

4. Cryo-preservation & storage

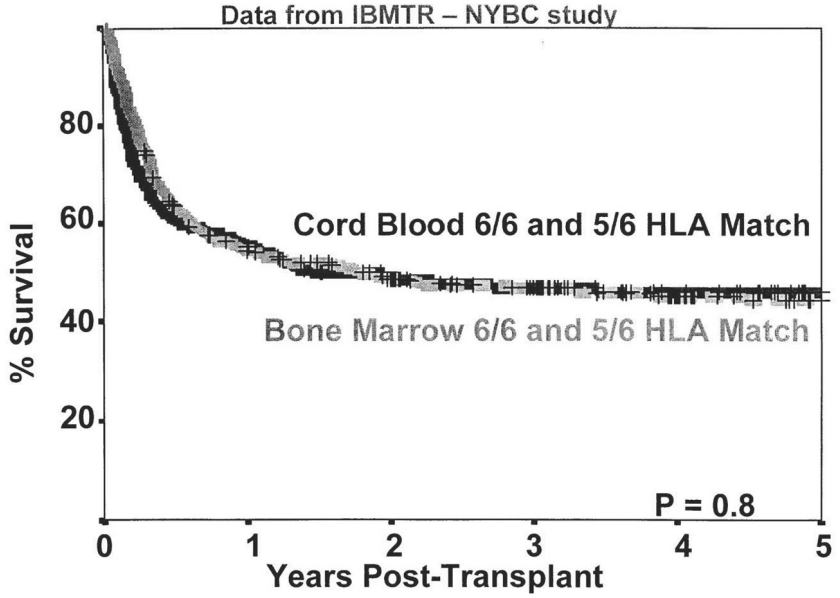
Research Results: Advantages of Cord Blood as a Clinical Source of Stem Cells *(Compared to bone marrow)*

- Cord Blood Donation poses no risks to donors
- No donor attrition: Well processed and stored grafts are good for many years
- Grafts are available on short notice (days)
- Less latent viral infection
- Less immune reaction against recipient: (lower graft-vs.-host reaction)
- Tolerance of mismatches: Easier to find useful matches for patients of all ethnic groups

The importance of CB TNC dose and HLA match for survival: US Patients - all diseases



5-Year Survival in US Children with Leukemia or Myelodysplasia



Bone Marrow Transplantation Today

(GAO Report, 2002)
(NMDP data)

1997-2000

44,740 Patients Needed Transplants

15,231 Preliminary NMDP Search

9,623 Formal NMDP Searches

4,056 Transplants
(<10% of need, 26.6% of searches)

"Typically requires many months,

Bone Marrow Transplantation: Ethnicity and Access to Transplants

* NMDP data, GAO Report, 2002

".. equal access to a match may not be attainable."

** NYBC research data

"Equal access to a match is attainable."

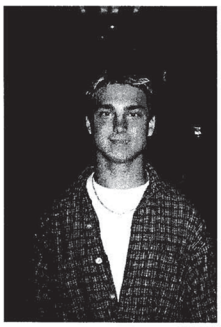
Ethnicity	Searches		Donors		Transplants	
	NMDP	NYBC	NMDP	NYBC	NMDP	NYBC
Asian	3.7%	3.6%	8%	6.7%	2.4%	4.0%
African American	12.1%	12.1%	10%	24.6%	6.3%	19.0%
Hispanic	12.5%	14.0%	11%	23.5%	7.8%	15.7%
Caucasian	69.1%	67.8%	67%	45.2%	81.9%	58.5%

First Human Cord Blood Transplant (Sibling)

Matthew 1988,

Age 6,

Fanconi Anemia



Matthew 2001,

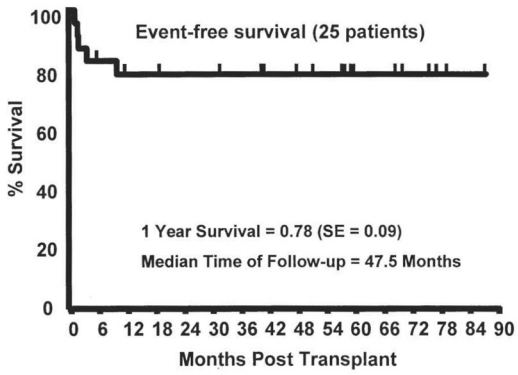
Age 19,

Healthy, attending college. Durably engrafted without adverse sequelae.

Research Results:
Applications of Unrelated Cord Blood Transplantation: 1993-2003

- **Hematologic malignancies**
  - Leukemia, lymphoma
- **Immunodeficiency diseases**
  - SCID, CID, CVID, WAS
- **Bone marrow failure syndromes**
  - Fanconi Anemia, Severe aplastic anemia
- **Hemoglobinopathies**
  - Sickle Cell Anemia
  - Thalassemia Major
- **Inborn errors of metabolism**
  - ADL, MLD, GLD
  - MPS I, II, III, VI
  - Tay Sachs Disease

Genetic Immunodeficiency Disease

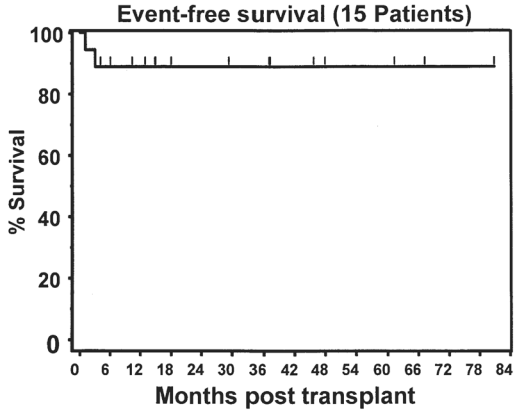


Transplanted for WAS
At age 18 months

Shown at 3 years
post transplant

Patients with SCID, CID, CVID, Wiscott Adrich Syndrome, Leukocyte Adhesion deficiency, etc. recover full immune function (both T and B cells) after unrelated cord blood transplantation.

Metabolic Disease
MPS-1 (Hurler Syndrome)

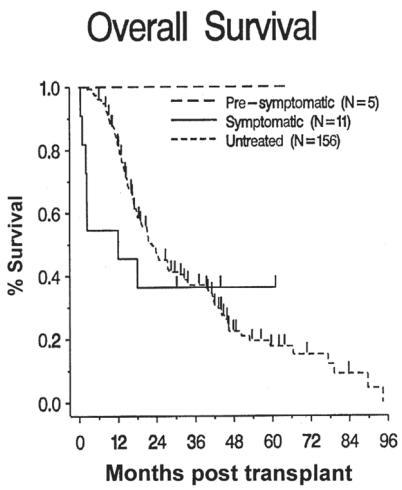


Transplanted with UCB
at 5 months of age

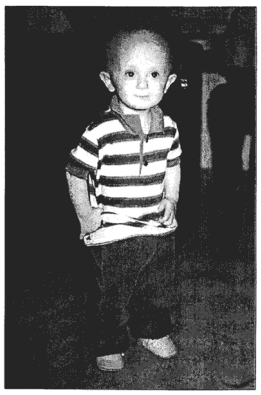
Shown at 6 years
post transplant
IQ147

CB transplant arrests progression and reverses damage in the cornea, liver, bones, cartilage, hearts and brains of young patients with Hurler Syndrome which otherwise causes death by 5-6 years of age.

Metabolic Disease
Krabbe Disease (Globoid Leukodystrophy)

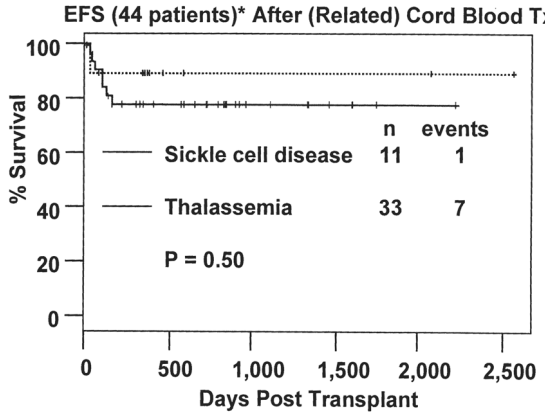


Transplanted at 3 weeks of age



This child is now neurologically normal at age 5. Two year old affected sibling died at age 2.

Genetic Disease
Sickle Cell Anemia & Thalassemia



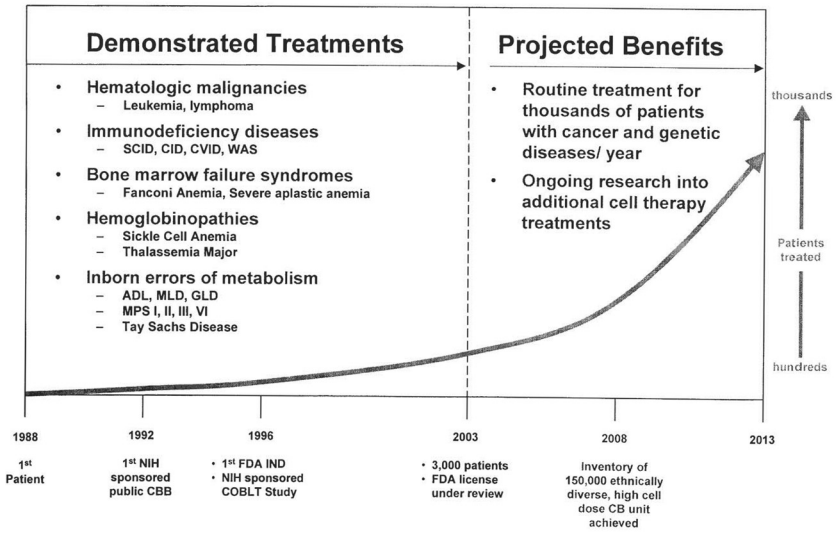
Unrelated CB Tx at 2.5 months

4 years Post Transplant for Thalassemia

Both related and unrelated cord blood transplants can successfully treat children with hemoglobinopathies, correcting the defect. If the transplant Is performed early in life, survivals are ≥80%.

* Blood; November 17, 2002

Summary



(PROPOSAL)
To Establish a National Cord Blood Bank

PURPOSE

- To provide well-matched grafts with good cell doses for patients of all ethnic groups
- To support cell therapy research with cord blood stem cells.

METHOD

- To create a network of 4-6 licensed U.S. cord blood banks that will build a public, high cell dose, ethnically balanced inventory of 150,000 units over 5 years, with federal support.

Senator BROWNBACK. Is there legislation introduced to do that, on either the House or the Senate side? Do you know?

Dr. KURTZBERG. There is one in progress, but it has not been introduced yet.

Senator BROWNBACK. OK.

Dr. KURTZBERG. There's a draft of a bill.

Senator BROWNBACK. All right. Because we'll sure want to get that out and do that for you. This is very encouraging. And if you were one of the parents of one of those children, this is the hope you've been looking for.

Dr. KURTZBERG. I've personally treated over 500 patients, and I have seen this work in children with otherwise fatal diagnoses. So it's very important to be able to continue the work.

Senator BROWNBACK. I'm sure that parents are absolutely ecstatic when they see that and see you. You're——

Dr. KURTZBERG. Sometimes.

Senator BROWNBACK.—an angel to them.

Dr. McDonald, thank you very much for joining us and for being here today.

STATEMENT OF JOHN W. MCDONALD, M.D., PH.D.
DEPARTMENT OF NEUROLOGY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

Dr. MCDONALD. Good afternoon, Mr. Chairman.

I'm Dr. John W. McDonald, and I'm an Assistant Professor at the Department of Neurology and Neurological Surgery and Director of the Spinal Cord Injury Program, at Washington University School of Medicine, in St. Louis. I'm also a staff physician at Barnes-Jewish Hospital, the Rehab Institute of St. Louis and St. Louis Children's Hospital.

I'm here today on behalf of the Coalition for the Advancement of Medical Research, a coalition of over 75 patient, scientific, and university organizations dedicated to ensuring that all forms of stem cell research be allowed to be explored here in the United States.

The Coalition started 2 years ago to ensure that stem cell research receives the same sorts of funding that all other research receives from the Federal Government. The group also is dedicated to ensuring that critical cutting-edge research is not criminalized.

As the Director of the Spinal Cord Injury Program, I see thousands of children and adults with devastating neurologic injuries, including spinal-cord injuries. These patients really have no practical alternatives for recovery of function after the injury has already occurred, such simple things as recovery of bowel and bladder control, or simply feeling a loved-one's embrace. And only some of the 11,000 people who are injured every year recover any substantial function with traditional rehabilitation, which assumes that recovery is only possible after 6 months to 2 years.

I'm currently working on a variety of ways to treat patients with spinal-cord injury or disease. And shown now is an example of a T2 weighted MRI image, the spinal cord is in the middle, if you see, down to the red box, it actually shows where the injury is. A really minute injury at this point in the nervous system becomes a really devastating problem. And I mentioned that there's 11,000 people injured each year. There's a quarter of a million living with spinal-cord injury, and another four to five times that many with medical causes of spinal-cord injury, such as multiple sclerosis or ALS.

I've been working on a variety of ways to treat patients with spinal-cord injury and disease. For example, I've seen significant improvements in a very small group of patients, using activity-based therapy. This is a therapy that relies on providing pattern activations for someone who's completely paralyzed, like putting a paralyzed person on a functional electrical stimulation bike, with this idea that the nervous system requires optimal activity in order for new cells to be born to optimize regeneration, now that we understand that the adult nervous system does have some limited capacity for regeneration.

Shown here on this graph is the results of a patient that participated in this. Now, let me preface this by saying that this individual was completely paralyzed, from the neck down, from just below C–2 down, unable to breathe, move, or feel below that level, for the first 5 years. Traditional history would say that there's no opportunity, absolutely, that this individual could regain any substantial function. And this individual began to recover substantial motor function, being able to move most of the joints in his body, to about 20 percent of normal on the scale. Of more importance was the recovery of sensation, which was about 70 percent of normal. Again, over the first 5 years, there was very limited recovery, and then a progressive recovery over the last 3 years, after institution of the activity-based recovery program, in the middle of 1999.

We've done additional research now in animals that demonstrates that this type of activity actually mobilizes the stem cells that are present in the spinal cord below the level of the injury. What happens, below the level of the injury, in a chronic situation, is that the number of stem cells are reduced, unable to be there to be able to replace cells that are lost. And this activity appears to be repleting those cells so that they're available, inasmuch as a stem cell transplant would allow.

Senator BROWNBACK. By the physical stimulation that's taking place.

Dr. MCDONALD. Right.

Now, while adult stem cells have potential for significantly improving clinical treatment of a wide range of diseases, I believe it's critical that we also explore the use of embryonic stem cells.

If you compare stem cells to a tree, adults stem cells have already developed and specialized down a particular path, or limb. On the other hand, embryonic stem cells are still at the base of the trunk, ready to be guided down any number of limbs. It's, therefore, much more feasible to try to encourage embryonic stem cells to develop into whatever cell type is needed.

As you can see from this video, this is an animal that's treated, 9 days after a spinal-cord injury, with embryonic stem cells that have been induced to become neuro progenitors. This is an animal that's just a control; treated identically, except no cells. You can see it has great difficulty moving its hind limbs, raising his tail, and basically drags his behind.

The next slide is a similar animal, but it's been transplanted with embryonic stem cells, and you can see, really, a marked improvement in its ability to walk, stand on its hind limbs, and lift his tail. And the stage at which these cells were transplanted were neuro progenitors similar to those that can be derived from ESLs.

So, as you can see from the video, we have already found encouraging support for the use of embryonic stem cells to cure or treat some of the most debilitating diseases. The two rats that you have just seen have the same injury, but the rat that received the transplanted embryonic stem cells has recovered significantly more use of its hind limbs and tail.

My hope is that one day the patients that I see in the Spinal Cord Injury Program will also be able to regain movement, just like that rat in this video.

And as a scientist, I cannot guarantee that embryonic stem cells will lead to cures and treatments. I can tell you, however, that they hold great promise. Science is a process in which we knock on 20 doors; 19 open, with nothing behind them; one opens to reveal a pot of gold. We can't predict which door will be the magic door.

The field of stem cell research, whether it be embryonic, adult, cord-blood stem cells, is extremely new. It's entirely too early to rule out any one of these areas of research in favor of another. But my wheelchair-bound patients should not have to wait for us to explore each possibility one at a time.

In the years that have been spent debating the issues here in Washington, research that could 1 day lead to cures and treatments for so many diseases has been held back. Some senior researchers have either left the United States to work elsewhere or have decided to work in other areas of biomedical research. And, more importantly, many of the next generation of researchers have decided to stay away from these areas because of the uncertain political environment.

Mr. Chairman, please allow all forms of stem cell research to move forward—adult, cord blood, and embryonic—so that we can continue to look for medicine's pot of gold.

Thank you.

[The prepared statement of Dr. McDonald follows:]

PREPARED STATEMENT OF JOHN MCDONALD, M.D., PH.D. ON BEHALF OF THE COALITION FOR THE ADVANCEMENT OF MEDICAL RESEARCH

Good afternoon Mr. Chairman and members of the Committee. I am Dr. John W. McDonald and I am an Assistant Professor in the Departments of Neurology, Neurological Surgery, Anatomy and Neurobiology and Director of the Spinal Cord Injury Program at Washington University School of Medicine in St. Louis. I am also a staff physician at Barnes-Jewish Hospital, the Rehabilitation Institute of St. Louis and St. Louis Children's Hospital.

I am here today on behalf of the Coalition for the Advancement of Medical Research,* a coalition of over 75 patient, scientific and university organizations dedicated to ensuring that all forms of stem cell research be allowed to be explored here in the United States. The Coalition started two years ago to ensure that stem cell research receives the same sorts of funding that all other research receives from the Federal government. The group also is dedicated to ensuring that critical, cutting-edge research is not criminalized.

As the director of the Spinal Cord Injury Program, I see thousands of children and adults with devastating spinal cord injuries. These patients have no real hope for recovering functions most of us take for granted, from bowel and bladder control to simply feeling a loved one's embrace. And only some of the 11,000 people who

*The Coalition is comprised of nationally-recognized patient organizations, universities, scientific societies, foundations, and individuals with life-threatening illnesses and disorders, advocating for the advancement of breakthrough research and technologies in regenerative medicine—including stem cell research and somatic cell nuclear transfer—in order to cure disease and alleviate suffering.

get injured each year recover with traditional rehabilitation, which assumes that recovery is only possible after six months to 2 years.

I am currently working on a variety of ways to treat patients with spinal cord injury or disease. For example, I've seen significant improvements in a very small group of patients using activity-based therapy, which relies on electrical stimulation to help patients exercise their paralyzed limbs. While significant, even those successes are minimal and extremely preliminary—it's still unclear whether these techniques can help most spinal cord injuries, and to what extent they alone can restore function. We *need* to examine other promising approaches, and I believe that embryonic stem cells have the most potential.

While adult stem cells also have potential for significantly improving clinical treatment of a wide range of diseases, I believe it is *critical* that we also explore the use of embryonic stem cells. If you compare stem cells to a tree, adult stem cells have already developed and specialized down a particular path, or limb. On the other hand, embryonic stem cells are still at the base of the trunk, ready to be guided down any of a number of limbs. It's therefore much more feasible to try to encourage embryonic stem cells to develop into whichever type of cell is needed.

As you can see from the video, we have already found encouraging support for the use of embryonic stem cells to cure or treat some of the most debilitating diseases. The two rats you see have the same injury, but the rat that received transplanted embryonic stem cells has recovered significantly more use of its hind legs and tail.

My hope is that one day the patients I see in the Spinal Cord Injury Program will also be able to regain movement, just like the rat in this video.

As a scientist, I cannot guarantee that embryonic stem cells *will* lead to cures and treatments. I can tell you, however, that they hold great promise. Science is a process in which we knock on 20 doors: Nineteen open with nothing behind them; One opens to reveal a pot of gold. We cannot predict which door will be that magic door. The field of stem cell research, whether it be embryonic, adult or cord blood stem cells, is still extremely new. It is entirely too early to rule out any one of these areas of research in favor of any other. My wheelchair bound patients should not have to wait for us to explore each possibility one at a time.

In the years that have been spent debating the issue here in Washington, research that could one day lead to cures and treatments for so many diseases has been held back. Some senior researchers have either left the United States to work elsewhere or have decided to work in other areas of biomedical research. And many of the next generation of researchers has decided to stay away for these areas because of the uncertain political environment. Mr. Chairman, please allow *all* forms of stem cell research to move forward, adult, cord-blood *and* embryonic, so that we can continue to look for medicine's pot of gold.

Senator BROWNBACK. Thank you, Dr. McDonald. And thank you for your passion and your heart and your work to help others be able to walk.

Dr. Peduzzi-Nelson, we have 12 minutes, I think, they're just telling me, left in the vote. So I think we'll try to get your testimony in before I head over to vote.

But I'm delighted to have you here, and please proceed with your testimony.

STATEMENT OF JEAN D. PEDUZZI-NELSON, PH.D.
DEPARTMENT OF PHYSIOLOGICAL OPTICS
UNIVERSITY OF ALABAMA AT BIRMINGHAM

Dr. PEDUZZI-NELSON. What I'm going to show is that these 20 doors are partially opened. We can see what doors contain the pots of gold and what doors contains gremlins that we need to close permanently. I agree with Dr. McDonald that we're not knocking on these doors equally. Even with the Federal ban, the vast majority of studies are still using embryonic animal stem cells and human stem cell lines. The ban does not affect animal stem cell research. Using a person's own stem cells is the area of research that's being neglected.

I would like to quickly review the results of some clinical and pre-clinical trials that clearly shows where the pots of gold are and where the gremlins are. We've already heard some testimony that there's definitely pots of gold for a number of children, using human umbilical cord blood, and also that the work that Dr. Hess presented, using bone marrow, and also Dr. McDonald's work with rehabilitative therapy—are all very viable, wonderful areas to pursue.

In terms of spinal-cord injury, I'd like to present the results of two clinical trials and show their results using an exact same test. In these trials, they were using tissue, neural tissue. And how this relates to the stem cell issue is, if you put this tissue—transplant it into the brain or spinal cord, the cells that survive are the stem cells, or the early derivatives of these stem cells.

In a clinical trial that took place at the University of Florida that began in 1997, minced fetal spinal-cord tissue was used. The results of the first two patients have been published and are presented on the left side of the first three graphs. Their finding was that there was very little change in their condition. However, in another study that's an ongoing trial in Portugal, person's own olfactory mucosa was used. All of the patients in this study, as you can see in the first graph, in the light-touch ASIA scores, and in the next graph, using the pin-prick ASIA scores, and in the next graph, using the motor scores, that there was some improvement in actually all the patients that received the transplant by the first month after the transplant of their own olfactory mucosa.

And furthermore, the first patient that was treated, after 15 months after—16 months after the treatment, regained bladder control. And I don't if many people in the audience know this, but this is a very severe problem with people with spinal-cord injury. And this woman no longer needs catheters at all.

What's interesting is, at the Portuguese studies, they had no rehabilitative methods available to them. There was no rehab therapy at all. The improvement was all what just happened naturally. And much greater improvement might have occurred if they had resources to have rehab therapy.

I'd like to move on to—in the next graph, to the results of two Parkinson's trials. These are clinical trials that clearly show some difference in the results. In a study by Freed and Associates done several years ago, human fetal stem cells were injected into the brain. And, on the left, you see the results of that study. There was a 28 percent improvement in the younger patients. "Younger," in this study, which I like, means less than 60 years old. However, at about 1 year after the transplant, there was a very devastating result in 15 percent of the patients. They got significantly worse because of overgrowth of these embryonic cells that were placed in the brain, and they were much worse in function than they had been previously.

However, there's been another clinical trial in Parkinson's, and this was using the person's own stem cells from their brain. And this was a study done by Dr. Michel Levesque, in California. In this case, in this patient, there was an 83 percent improvement, and the patient had the treatment 2 years, and no detrimental side effects have been observed.

The experimental studies, animal studies, also provide indication of what is behind the doors. First, in the next slide, it's true, maybe you can't make a whole tree from adult neural stem cells, the cells that are from the brain. However, there's lots of other stem cells in the body. So why would you even try to make every stem cell from an adult neural stem cell?

Also, we know that you can make neurons, muscle cells, blood cells, from the stem cells in the adult brain. Also, you can get neurons or nerve cells or support cells to develop from bone, as Dr. Hess has mentioned, from skin, from blood, and my favorite, from fat stem cells.

Second, the experimental studies that have been done using embryonic stem cells, as do the clinical trials, show that embryonic stem cells are dangerous, especially in terms of overgrowth. And studies by Bjourland and also by Dr. Gage and others have found tumor formation and sometimes blockage of the ventricular system can occur using embryonic stem cells.

Third, my own work in rats with chronic severe spinal-cord injury show that adult stem cells can lead to a functional improvement.

I think that it really gets down to a very basic question. If you or your loved one had a serious disease or injury, would you like them, or yourself, to receive your own stem cells or fetal, embryonic, or cloned stem cells? I think you don't have to be a scientist to answer that question. But the answer to the question is also supported by the clinical trials and the pre-clinical animal trials that have been done so far.

I would like to end by saying that the reason I'm here is that the victims of terrible diseases and injuries are again becoming victims to support a therapy that's not in their best interest. With only a limited amount of funding available, more focus is needed in directing research in areas that can help people in the next five to 10 years, not several lifetimes away.

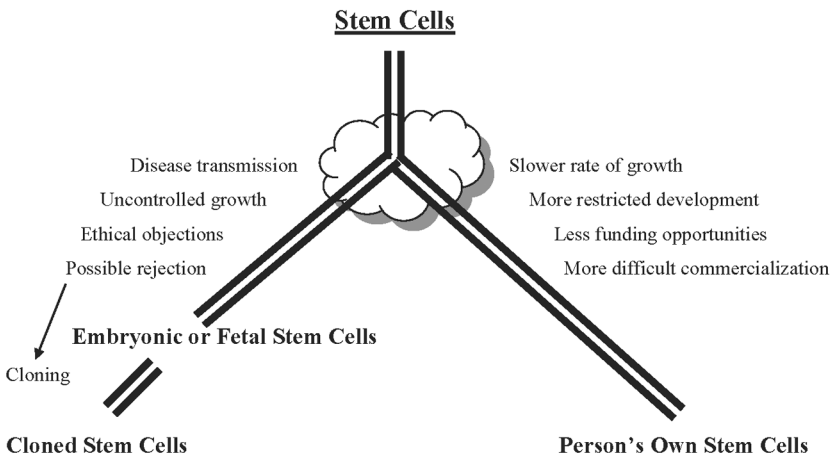
Thank you.

[The prepared statement of Dr. Peduzzi-Nelson follows:]

PREPARED STATEMENT OF JEAN D. PEDUZZI-NELSON, PH.D., DEPARTMENT OF PHYSIOLOGICAL OPTICS, UNIVERSITY OF ALABAMA AT BIRMINGHAM

"THE Y IN THE ROAD"

Thank you Senator Brownback and Senator McCain and distinguished senators of the subcommittee for the invitation to present to you today. Stem cells are a major medical breakthrough with tremendous potential but we are now at a *"Y in the road"* as far as the future of medicine. In deciding our course, the way is clouded by opposing ethical views, vested interests of certain scientists & the biotech community, political allegiances and celebrities. I would like the members of the subcommittee and the audience to set aside all those factors for just a few minutes. I ask you now to think about a very basic question: *If your loved one was suffering from a terrible injury or disease, what type of stem cell treatment do you think would work the best: (1) their own cells or (2) cells derived from embryos, fetuses or cloned embryonic cells?* I don't think you need to be a scientist to answer that question. It also turns out that if you look at the scientific evidence, not speculation about the future by prominent scientists on either side of the issues, but just the facts of where we are today based on clinical and preclinical trials, the logical choice in medical treatment is also the best medical treatment.



Treatments for Wide Variety of Diseases and Injuries

I would now like to review the scientific data that prove that an intuitively obvious concept is **also** supported by the results of recent clinical trials and preclinical trials (experimental animal studies). First, I would like to review the clinical trials using stem cells and their derivatives in spinal cord injury and Parkinson's disease. Two clinical trials using fetal tissue have been done in the U.S. and one on-going clinical trial in Portugal using a person's own tissue. All of these spinal cord injury trials are important to the question of stem cell research because the cells that survive after the tissue transplant are the stem cells and their early derivatives. The mature cells in the tissue except for some support cells would die off. The first study using fetal tissue was done at the University of Florida, beginning in 1997, in the treatment of syringomelia—a condition in which a large cavity forms in the spinal cord. Minced spinal cords (SC) from 4–8 different human fetuses taken from elective abortions were grafted into the cavity in the spinal cord. At 18-month follow-up of the first 2 patients, the condition of the patients was not very different.[1] Another study was performed more recently using pig fetal tissue at Washington University and SUNY/Albany. There have been no further announcements regarding this study although the first patient was done in April 2001.[2] The study in Portugal has had impressive results using a person's own olfactory mucosa.[3] The olfactory mucosa lines the upper nasal cavity and contains stem cells and cells that encourage growth of nerve cell processes called olfactory ensheathing cells. Patients with severe (complete) spinal cord injuries were operated at 6 months following the injury. Other patients in this study (not reported below) were up to 7 years post-injury with similar or better results. On the next page are the charts comparing the results from the first 2 patients from each of the 2 different trials. In comparing the results of using embryonic tissues or using one's own tissue:

(1) There was little change in the condition of the patients using the embryonic tissue. There appeared to be no massive rejection even though 4–8 different embryos were used for each patient in the University of Florida trial and no reports of rejection in the trial using pig cells used in Washington University and SUNY/Albany.

(2) In the Portuguese study, there were increases in motor and/or sensory scores by 1 month in almost all the patients receiving their own olfactory mucosa suggesting that a person's own tissue is more effective. The first patient done regained bladder control at 16 months after the treatment and no longer uses

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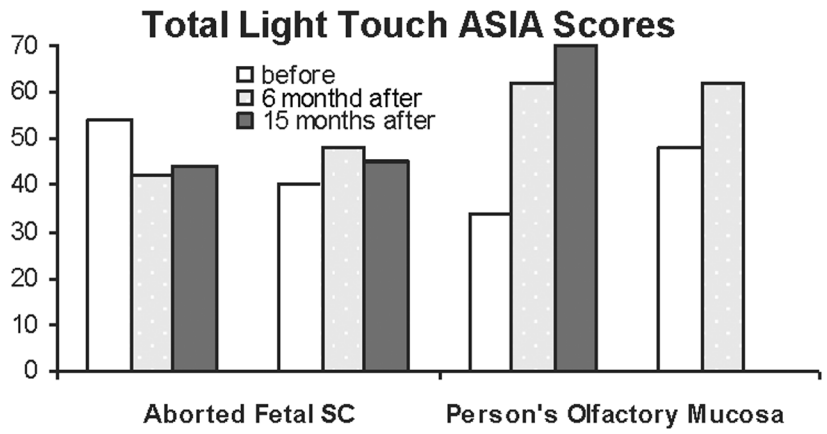
[1] Wirth E.D. 3rd, Reier P.J., Fessler R.G., Thompson F.J., Uthman B., Behrman A., Beard J., Vierck C,J., Anderson D.K. Feasibility and safety of neural tissue transplantation in patients with syringomyelia.Journal of Neurotrauma. 18(9):911–29, 2001.

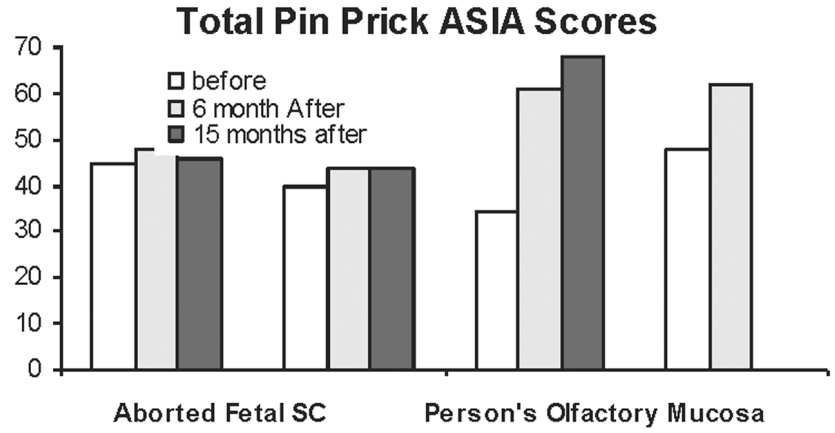
[2] *http://www.diacrin.com/SCI%20Albany%20Surg.htm*

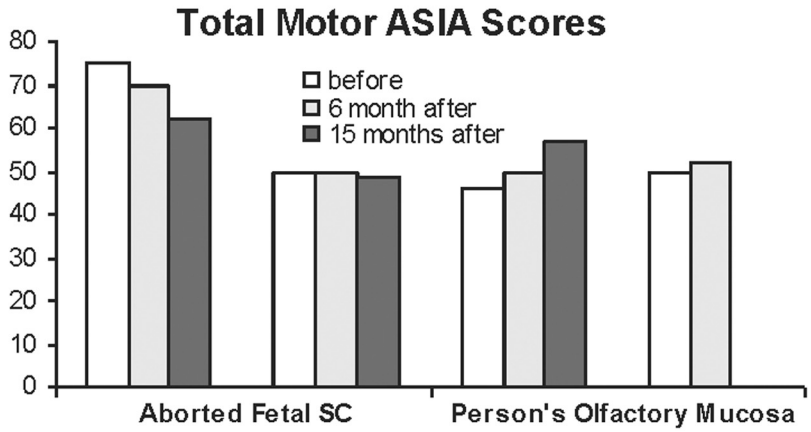
[3] Parks, D. Birmingham, News, Sunday, December 8, 2002, Olfactory nerves could help mend spinal injuries. *http://www.scsnw.com/Nerves%20in%20nose%20may%20repair%20spinal%20cord%20injuries.htm*

catheters. The second patient that had less improvement was the patient that had the largest lesion (6 cm) of all of the patients done so far.

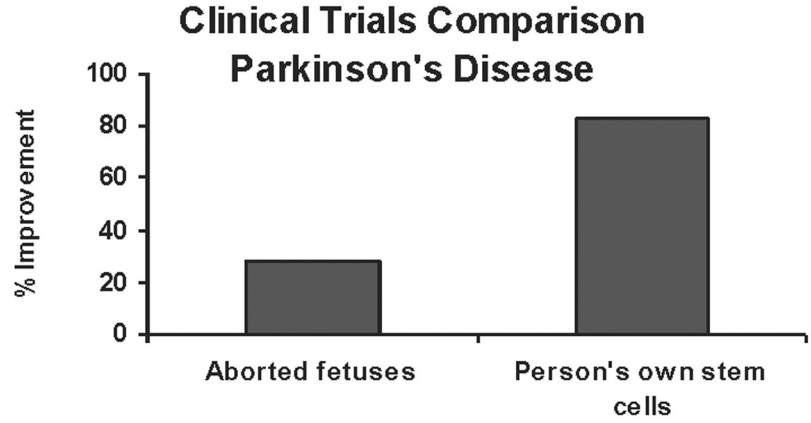
The changes observed might have been greater for the patients treated in Portugal if rehabilitative therapy was available there.







The clinical trials in Parkinson's disease had dramatic differences in their findings depending on the original source of the cells: fetuses or the person's own cells. In both cases, the cells were matured in culture before being transplanted into the patient. A clinical trial was done by Dr. Freed and colleagues in which 19 patients received cells derived from 4 different fetuses with abortions at 7–8 weeks after conception.[4] The patients that were under 60 years showed about a 28 percent improvement in the Unified Parkinson's Disease Rating Scale (UPDRS). About 15 percent of these patients showed severe decline in function at 1 year after treatment. In another Parkinson's study done by Dr. Michel Levesque, the patient who was 57 years old at the time of treatment, received cells derived from his own brain stem cells.[5] This patient showed an 83 percent improvement in the UPDRS. Below is a chart that summarizes the percentage improvement in the 2 clinical trials.



The greater improvement and lack of harmful late effects using a person's own cells is primarily due to the fact that the cells were derived from an adult as opposed to fetuses. Of lesser contribution to the overall improvement probably was that the cells were genetically identical and not rejected. There was no evidence of

[4] Freed C.R., Greene P.E., Breeze R.E., Tsai W.Y., DuMouchel W., Kao R., Dillon S., Winfield H., Culver S., Trojanowski J.Q., Eidelberg D., Fahn S. (2001) Transplantation of embryonic dopamine neurons for severe Parkinson's disease. New Engl. J. Med.. 344:710–9.

[5] Levesque, M.F. and T. Neuman Autologous transplantation of adult human neural stem cells and differentiated dopaminergic neurons for Parkinson's disease: one year post-operative clinical and functional metabolic results. AANS31, 2002.

massive rejection in any of the studies using fetal cells/tissues, even when pig cells were used without long-term immune-suppressing drugs to prevent rejection. However, better results were obtained using person's own adult cells. The study by Freed and colleagues also suggests that the primary problem with the fetal cells is not rejection. Using cells derived from fetuses, the severe functional deterioration seen in several patients was due to overgrowth of the cells derived from fetuses, not a lack of cell survival.

It is rather ironical that the qualities cited for the superiority of embryonic or fetal stem cells are actually responsible for causing problems. Rapid growth is not always a desirable quality as clearly seen with weeds in a garden or cancer in the body. In the Parkinson's study, cells derived from the embryo and the adult were both allowed to mature in culture, but the end result was quite different. As the graph demonstrates, the patient's own cells markedly improved and no debilitating side effects were observed. A possible explanation for these findings is that adult stem cells are the natural components of the adult body and endogenous mechanisms exist to control their growth and maturation to replace damaged neurons.[6] The cells from the adult may have certain molecules on their surface (ligands or receptors) that keeps the cells from uncontrolled growth. Both studies allowed the stem cell to mature before implantation. If maturation of stem cell is a necessary safety step, then the fact that embryonic cells are so immature is a disadvantage. It would be possible and simpler to have large-scale commercialization of cells derived from embryos or fetuses but the end product would be grossly inferior for the recipients. There are many types of adult human stem cells that are readily available that lack the problems of overgrowth, rejection, and disease transmission. Most people do not need a total body replacement. Even if costly and complicated procedures of cloning are done to produce the human stem cells (not technically possible yet), the cells will not be genetically identical because of the mitochondrial DNA and improper imprinting. There is evidence that the debate is raging in the scientific community. A recent scientific article describing a clinical trial included an opinion that the authors, although using a patient's own blood stem cells, in no way support a ban on using human embryonic stem cells.[7]

Preclinical Trials: Preclinical trials (experimental animal studies) not only provide the basis for future clinical trials described above, but also support the same conclusion that is reached in reviewing the clinical trials. There is abundant evidence that adult stem cells can be used as a therapy and are readily available in people. The conclusion from the preclinical studies is that adult stem cells work just as well, if not better, than embryonic stem cells and are probably safer.[8] There is no need for embryonic stem cells especially cloned ones.

Ten years ago, it was discovered that stem cells exist in the adult brain and spinal cord and can be readily isolated.[9] [10] Many initial ideas about adult stem cells in the brain were wrong. For example, the cells were first thought to only be present in rodents, but later found in people.[11] It was once thought that only embryonic stem cells have the capacity to become many different cell types. More recently, it has been found that neural stem cells from adults have this potential.[12] Stem cells and their cellular derivatives may be useful in many ways. In the nervous system, they can be replacement neurons, source of growth factors, or a substrate of growth. Another misconception was that adult stem cells might not be functional in their ability to transmit a signal to another neuron. There is recent evidence that adult stem cells can mature and form functional connections with other neurons in cul-

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[6] van Praag H. Schinder A.F. Christie B.R. Toni N. Palmer T.D. Gage F.H. Functional neurogenesis in the adult hippocampus. Nature. 415(6875):1030–4, 2002.

[7] Janson C.G., T.M. Ramesh, M.J. During, P. Leone and J. Heywood 2001 Human intrathecal transplantation of peripheral blood stem cells in amyotrophic lateral sclerosis. J Hematotherapy & Stem Cell Res 10:93–915.

[8] Bjorklund L.M.. Sanchez-Pernaute R.. Chung S.. Andersson T.. Chen I.Y.. McNaught K.S.. Brownell A.L.. Jenkins B.G.. Wahlestedt C.. Kim K.S.. Isacson O. Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. [comment]. [Journal Article] Proceedings of the National Academy of Sciences of the United States of America. 99(4):2344–9, 2002.

[9] Reynolds B.A., Wiess S. 1992. Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science 255:1701–1710.

[10] Richards, Lric T.J., Bartlett P.F. 1992. De nonv generation of neuronal cells from the adult mouse brain. Proc. Natl Acad Sci USA 89:8591–8595.

[11] Eriksson P.S., Perfilieva E., Bjork-Eriksson, T., Alborn A.M., Nordborg C., Peterson D.A., Gage F.H. 1998. Neurogenesis in the adult human hippocampus. Nat Med. 4:13113–1317.

[12] Gritti A., Vescovi A.L., Galli R. Adult neural stem cells: plasticity and developmental potential. Journal of Physiology-Paris. 96(1–2):81–90, 2002.

ture.[13] [14] A surprising finding was that many cells in the adult (not just the cells in the brain and spinal cord) have the potential to be neurons. Sources of adult human stem cells that are capable of forming neurons include the brain,[15] [16] olfactory mucosa in the upper nose,[17] [18] cornea,[19] choroid and sclera[20] of the eye, teeth,[21] bone marrow.[22] [23] and skin.[24] Further evidence that bone marrow can be a source of neurons for the brain is supported by findings in the patients' brains who have received bone marrow transplants.[25] There is no reason to use embryonic/fetal tissue or to clone people to obtain genetically similar embryonic stem cells when there is a ready supply of stem cells in adult humans.

There are several studies that support the usefulness of adult stem cells. Stem cells obtained from adult spinal cord have been shown to survive and mature into neurons when transplanted into the brain.[26] Transplantation of stem cells from adult human brain causes myelination to occur in a focally demyelinated spinal cord of the rat.[27] Demyelination is common in spinal cord injury and disease states such as Multiple Sclerosis, and interferes with signal conduction between the neurons. Human cells from adult have been used to treat animal models of disease states . For example, human cells led to functional improvement in animal models of Parkinson's disease using human bone cells[28] or using neural stem cells.[29] Human brain adult stem cells can even be obtained after death[30] so if a person's own stem cells are not used; there are other less objectionable alternatives. Another alternative to the use of embryonic stem cells is human umbilical cord blood. Human

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[13] Toda H., Takahashi J., Mizoguchi A., Koyano K., Hashimoto N., Neurons generated from adult rat hippocampal stem cells form functional glutamatergic and GABAergic synapses in vitro. Experimental Neurology. 165(1):66–76, 2000.

[14] Song, H-j, C.F. Stevens, F.H. Gage, Neural stem cells from adult hippocampus develop essential properties of functional CNS neurons. Nature Neuroscience5: 438–445, 2002.

[15] Suslov O.N., Kukekov V.G., Ignatova T.N., Steindler D.A. Neural stem cell heterogeneity demonstrated by molecular phenotyping of clonal neurospheres. Proceedings of the National Academy of Sciences of the United States of America. 99(22):14506–11, 2002.

[16] Akiyama Y., Honmou O., Kato T., Uede T., Hashi K., Kocsis J.D. Transplantation of clonal neural precursor cells derived from adult human brain establishes functional peripheral myelin in the rat spinal cord. Experimental Neurology. 167(1):27–39, 2001.

[17] Murrell W., Bushell G.R., Livesey J., McGrath J., MacDonald K.P., Bates P.R., Mackay-Sim A. Neurogenesis in adult human. NeuroReport. 7(6):1189–94, 1996.

[18] Feron F.. Perry C., McGrath J.J., Mackay-Sim A. New techniques for biopsy and culture of human olfactory epithelial neurons. Archives of Otolaryngology—Head & Neck Surgery. 124(8):861–6, 1998.

[19] Seigel G.M., Sun W., Salvi R., Campbell L.M., Sullivan S., Reidy J.J. Human corneal stem cells display functional neuronal properties. Molecular Vision. 9:159–63, 2003.

[20] Arsenijevic Y., Taverney N., Kostic C., Tekaya M., Riva F., Zografos L., Schorderet D., Munier F. Non-neural regions of the adult human eye: a potential source of neurons?. Investigative Ophthalmology & Visual Science. 44(2):799–807, 2003.

[21] Miura M., Gronthos S., Zhao M., Lu B., Fisher L.W., Robey P.G., Shi S. SHED: Stem cells from human exfoliated deciduous teeth. Proceedings of the National Academy of Sciences of the United States of America. 100(10):5807–12, 2003.

[22] Deng W., Obrocka M., Fischer I., Prockop D.J. In vitro differentiation of human marrow stromal cells into early progenitors of neural cells by conditions that increase intracellular cyclic AMP. Biochemical & Biophysical Research Communications. 282(1):148–52, 2001.

[23] Hung S.C., Cheng H., Pan C.Y., Tsai M.J., Kao L.S., Ma H.L. In vitro differentiation of size-sieved stem cells into electrically active neural cells. Stem Cells. 20(6):522–9, 2002.

[24] Toma J.G., Akhavan M., Fernandes K.J., Barnabe-Heider F., Sadikot A., Kaplan D.R., Miller F.D. Isolation of multipotent adult stem cells from the dermis of mammalian skin. Nature Cell Biology. 3(9):778–84, 2001.

[25] Mezey E., Key S., Vogelsang G., Szalayova I., Lange G.D., Crain B.Transplanted bone marrow generates new neurons in human brains. Proceedings of the National Academy of Sciences of the United States of America. 100(3):1364–9, 2003.

[26] Shihabuddin L.S., Horner P.J., Ray J., Gage F.H. Adult spinal cord stem cells generate neurons after transplantation in the adult dentate gyrus. Journal of Neuroscience. 20(23):8727–35, 2000.

[27] Akiyama Y., Honmou O., Kato T., Uede T., Hashi K., Kocsis J.D.: Transplantation of clonal neural precursor cells derived from adult human brain establishes functional peripheral myelin in the rat spinal cord. Exp Neurol 167:27–39, 2001.

[28] Hou L.L., Zheng M., Wang D.M., Yuan H.F., Li H.M., Chen L., Bai C.X., Zhang Y., Pei X.T.[Migration and differentiation of human bone marrow mesenchymal stem cells in the rat brain].Sheng Li Hsueh Pao—Acta Physiologica Sinica. 55(2):153–9, 2003.

[29] Liker M.A., Petzinger G.M., Nixon K., McNeill T., Jakowec M.W. Human neural stem cell transplantation in the MPTP-lesioned mouse. Brain Research. 971(2):168–77, 2003.

[30] Palmer T.D., Schwartz P.H., Taupin P., Kaspar B., Stein S.A., Gage F.H. Cell culture. Progenitor cells from human brain after death. Nature. 411(6833):42–3, 2001.

umbilical cord blood has the potential to form neurons,[31] [32] as well as other cell types.[33] Human umbilical cord blood injected IV caused a functional improvement when injected into experimental animals with traumatic brain injury or stroke.[34] [35] In the case of genetic defects, there are several other alternatives to cloning. One is gene therapy that has been successfully used in mice[36] and humans. More recently stem cells have been used as vehicle to deliver genes to the brain.[37] [38] [39] [40]. Bone marrow stromal cells from adult rats promote functional recovery after spinal cord injury in rats when given 1 week after injury,[41] even when the cells are injected intravenously.[42] Bone marrow stromal cells also will migrate to site of a head injury when given IV and caused a functional improvement.[43]

Below is a brief summary (in italics) of recent findings using other treatments besides stem cell for injuries and diseases of the nervous system. This summary is meant to make 2 major points:

(1) Other treatments used alone or in combination with adult stem cells may hold the greatest promise in treating spinal cord injury and other damage to the nervous system.

(2) While there is no ban on animal cloning, a review of recent literature revealed more than 40 articles of promising treatments other than stem cells for spinal cord injury but only 1 or just a few articles showing any therapeutic benefit of therapeutic cloning. The one article that received significant press coverage attempted to show a benefit of cloning in an animal study also revealed some of the difficulties with this procedure.[44]

Other cell types: Other cell types that do not form neurons also help in recovery. After selective demyelination in rat spinal cord, olfactory ensheathing cells myelinated axons[45] and led to greater motor and somatosensory evoked potentials and a better functional outcome.[46] Olfactory ensheathing cells promote locomotor re-

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[31] Sanchez-Ramos J.R., Song S., Kamath S.G., Zigova T., Willing A., Cardozo-Pelaez F., Stedeford T., Chopp M., Sanberg P.R. Expression of neural markers in human umbilical cord blood. Experimental Neurology. 171(1):109–15, 2001.

[32] BuzaAska L., Stachowiak E., Stachowiak M., DomaAska-Janik K. Neural stem cell line derived from human umbilical cord blood—morphological and functional properties.Journal of Neurochemistry. 85 Suppl 2:33, 2003.

[33] Goodwin H.S., Bicknese A.R., Chien S.N., Bogucki B.D., Quinn C.O., Wall D.A. Multilineage differentiation activity by cells isolated from umbilical cord blood: expression of bone, fat, and neural markers. Biology of Blood & Marrow Transplantation. 7(11):581–8, 2001.

[34] Lu D., Sanberg P.R., Mahmood A., Li Y., Wang L., Sanchez-Ramos J., Chopp M. Intravenous administration of human umbilical cord blood reduces neurological deficit in the rat after traumatic brain injury.Cell Transplantation. 11(3):275–81, 2002.

[35] Sanberg P.R., Chopp M., Willing A.E., Zigova T., Saporta S., Song S., Bickford P., Garbuzova-Davis S., Newman M., Cameron D.F., Sanchez-Ramos J. Potential of umbilical cord blood cells for brain repair.Journal of Neurochemistry. 81 Suppl 1:83, 2002.

[36] Shen J.S., Watabe K., Ohashi T., Eto Y. Intraventricular administration of recombinant adenovirus to neonatal twitcher mouse leads to clinicopathological improvements. Gene Therapy. 8(14):1081–7, 2001.

[37] Schwarz E.J., Reger R.L., Alexander G.M., Class R., Azizi S.A., Prockop D.J. Rat marrow stromal cells rapidly transduced with a self-inactivating retrovirus synthesize L–DOPA in vitro. Gene Therapy. 8(16):1214–23, 2001.

[38] Nakano K., Migita M., Mochizuki H., Shimada T. Differentiation of transplanted bone marrow cells in the adult mouse brain. Transplantation. 71(12):1735–40, 2001.

[39] Park K.W., Eglitis M.A., Mouradian M.M. Protection of nigral neurons by GDNF-engineered marrow cell transplantation. Neuroscience Research. 40(4):315–23, 2001.

[40] Ehtesham M., Kabos P., Gutierrez M.A., Chung N.H., Griffith T.S., Black K.L., Yu J.S. Induction of glioblastoma apoptosis using neural stem cell-mediated delivery of tumor necrosis factor-related apoptosis-inducing ligand. Cancer Research. 62(24):7170–4, 2002l.

[41] Hofstetter C.P., Schwarz E.J., Hess D., Widenfalk J., El Manira A., Prockop D.J., Olson L. Marrow stromal cells form guiding strands in the injured spinal cord and promote recovery. Proceedings of the National Academy of Sciences of the United States of America. 99(4):2199–204, 2002.

[42] Akiyama Y., Radtke C., Honmou O., Kocsis J.D. Remyelination of the spinal cord following intravenous delivery of bone marrow cells. [Journal Article] GLIA. 39(3):229–36, 2002.

[43] Lu D., Mahmood A., Wang L., Li Y., Lu M., Chopp M. (2001) Adult bone marrow stromal cells administered intravenously to rats after traumatic brain injury migrate into brain and improve neurological outcome. Neuroreport 12:559–63.

[44] Rideout W.M. III, Hochedlinger K., Kyba, M. Daley Q., and Jaenisch R. Correction of a genetic defect by nuclear transplantation and combined cell and gene therapy Cell 109:17–27

[45] Kato T., Honmou O., Uede T., Hashi K., Kocsis J.D. Transplantation of human olfactory ensheathing cells elicits remyelination of demyelinated rat spinal cord. GLIA. 30(3):209–18, 2000.

[46] VerdA E., GarcA-a-AlA-as G., ForA(C)s J., LA pez-Vales R., Navarro X. Olfactory ensheathing cells transplanted in lesioned spinal cord prevent loss of spinal cord parenchyma and promote functional recovery GLIA. 42(3):275–86, 2003.

covery in the transected cord after delayed transplantation.[47] These cells were also found to stimulate growth of motor axons.[48] Olfactory ensheathing cells when used with methylprednisolone promoted functional recovery and axonal regeneration after lesioning of the corticospinal tract.[49]

Growth Factors: With the discovery of new growth factors such as neurotrophic factors and cytokines that influence the survival and growth of neurons, it was hoped that spinal cord injury could soon be treated. Brain-derived neurotrophic factor (BDNF) reduces the necrotic zone and supports neuronal survival after spinal cord hemisection in adult rats[50] and suppresses apoptosis of oligodendrocytes.[51] Also neurotrophin-3 (NT–3) enhances sprouting of corticospinal tract after adult spinal cord lesion[52] even in chronic SCI.[53] Basic fibroblast growth factor (bFGF) reduced the pathology observed in spinal cord injured rats receiving bFGF via the CSF following a spinal cord injury.[54] Acidic fibroblast growth factor (aFGF) promote axonal growth between spinal cord slices[55] and when combined with peripheral nerve segments led to improved locomotor function after spinal transection.[56] Insulin growth factor 1 (IGF–1) stimulates myelin formation in the nervous system[57] and also stimulates the production of neurons and synapse formation.[58] In our own lab studies using cells derived from adult stem cells to treat rats with severe, chronic spinal cord injuries, significant functional improvement was observed when the factors (diff media) used for stem cells maturation are used alone. Further improvements are found when adult stem cell (SC) or IGF–1 is added to the treatment suggesting the benefit of combination treatments.

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[47] Lu J., Feron F., Mackay-Sim A., Waite P.M. Olfactory ensheathing cells promote locomotor recovery after delayed transplantation into transected spinal cord. Brain 125:14–21, 2002.

[48] Ramon-Cueto A., Cordero M.I., Santos-Benito F.F., Avila J. Functional recovery of paraplegic rats and motor axon regeneration in their spinal cords by olfactory ensheathing glia. Neuron 2000 Feb;25(2):425–35.

[49] Nash H.H., Borke R.C., Anders J.J. Ensheathing cells and methylprednisolone promote axonal regeneration and functional recovery in the lesioned adult rat spinal cord. Journal of Neuroscience. 22(16):7111–20, 2002.

[50] Novikova L., Novikov L., Kellerth J.O. Brain-derived neurotrophic factor reduces necrotic zone and supports neuronal survival after spinal cord hemisection in adult rats. Neuroscience Letters. 220(3):203–6, 1996.

[51] Koda M., Murakami M., Ino H., Yoshinaga K., Ikeda O., Hashimoto M., Yamazaki M., Nakayama C., Moriya H. Brain-derived neurotrophic factor suppresses delayed apoptosis of oligodendrocytes after spinal cord injury in rats. Journal of Neurotrauma. 19(6):777–85, 2002.

[52] Schnell, L., R. Schneider, R. Kolbeck, Y.A. Bard and M.E. Schwab (1994) Neurotrophin-3 enhances sprouting of corticospinal tract during development and after adult spinal cord lesion. Nature 367:170–173.

[53] Tuszynski M.H., Grill R., Jones L.L., Brant A., Blesch A., L.A. w K., Lacroix S., Lu P. NT–3 gene delivery elicits growth of chronically injured corticospinal axons and modestly improves functional deficits after chronic scar resection. Experimental Neurology. 181(1):47–56, 2003.

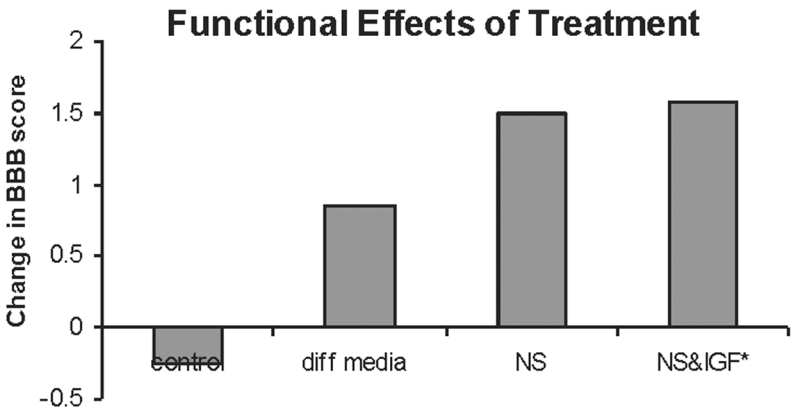
[54] Liu W.G., Luo Y.X. The early protective effects of basic fibroblast growth factor on acute spinal cord injury in rats. [Chinese]Chung-Kuo Hsiu Fu Chung Chien Wai Ko Tsa Chih/Chinese Journal of Reparative & Reconstructive Surgery. 13(5):291–4, 1999.

[55] Lee Y.S., Baratta J., Yu J., Lin V.W., Robertson R.T. AFGF promotes axonal growth in rat spinal cord organotypic slice co-cultures. Journal of Neurotrauma. 19(3):357–67, 2002.

[56] Lee Y.S., Hsiao I., Lin V.W. Peripheral nerve grafts and aFGF restore partial hindlimb function in adult paraplegic rats. Journal of Neurotrauma. 19(10):1203–16, 2002.

[57] Brooker G.J., Kalloniatis M., Russo V.C., Murphy M., Werther G.A., Bartlett P.F. Endogenous IGF–1 regulates the neuronal differentiation of adult stem cells. J. Neurosci. Res. 59(3):332–41, 2000.

[58] O'Kusky J.R., Ye P., D'Ercole A.J. Insulin-like growth factor-I promotes neurogenesis and synaptogenesis in the hippocampal dentate gyrus during postnatal development. Journal of Neuroscience. 20(22):8435–42, 2000.



Another cytokine, transforming growth factor-beta (TGF-beta) caused a decrease in the lesion size following SCI.[59] Yet another cytokine, glial cell line-derived neurotrophic factor (GDNF) when incorporated in a fibrin glue promotes dorsal root regeneration into spinal cord.[60] Metabolites such as inosine also appear to encourage growth of spared axons and possibly injured axons following spinal cord injury.[61] The spinal cord distal to the injury consists of cells that are shrunken and appear unhealthy. One possibility is that this natural metabolite especially when used as part of a combination treatment may stimulate the growth of these cells. Many recent studies have used a combination of growth factors. The combination of EGF and bFGF showed better functional recovery than vehicle or either factor alone.[62] Insulin-like growth factor (IGF) and epidermal growth factor (EGF) rescued motor neurons better than each individually even when delivered after 4-week delay.[63] Although significant stimulation of axonal growth is observed with growth factors, problems in delivery, penetration, and down-regulation or truncation of receptors[64] have perhaps kept their full potential from being realized.

Gene therapies: To overcome the problem of the growth factors actually reaching the affected neurons, two strategies have been taken. First, certain cell types have been modified to produce growth factors then grafted into the injury site. Second, endogenous cells have been genetically modified primarily using virus vectors. Fibroblasts genetically modified to produce BDNF[65] or NGF[66] support regrowth of chronically injured axons. The in vivo transfer of GDNF cDNA can promote axonal regeneration and enhance locomotion functional recovery.[67] Neurotrophin-secreting Schwann cell implants improved urinary bladder structure after spinal cord contu-

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[59] Tyor W.R., Avgeropoulos N., Ohlandt G., Hogan E.L. Treatment of spinal cord impact injury in the rat with transforming growth factor-beta. Journal of the Neurological Sciences. 200(1–2):33–41, 2002.

[60] Iwakawa M., Mizoi K., Tessler A., Itoh Y. Intraspinal implants of fibrin glue containing glial cell line-derived neurotrophic factor promote dorsal root regeneration into spinal cord. Neurorehabilitation & Neural Repair. 15(3):173–82, 2001.

[61] Benowitz L.I., D.E. Goldberg, J.R. Madsen, D. Soni and N. Irwin Inosine stimulates extensive axon collateral growth in the rat corticospinal tract after injury. PNAS 96: 13486–13490, 1999.

[62] Kojima A., Tator C.H. Intrathecal administration of epidermal growth factor and fibroblast growth factor 2 promotes ependymal proliferation and functional recovery after spinal cord injury in adult rats. Journal of Neurotrauma. 19(2):223–38, 2002.

[63] Bilak M.M., Kuncl R.W. Delayed application of IGF–I and GDNF can rescue already injured postnatal motor neurons. Neuroreport. 12(11):2531–5, 2001.

[64] Liebl D.J., Huang W., Young W., Parada L.F. Regulation of Trk receptors following contusion of the rat spinal cord.Experimental Neurology. 167(1):15–26, 2001.

[65] Jin Y., Tessler A., Fischer I., Houle J.D. Fibroblasts genetically modified to produce BDNF support regrowth of chronically injured serotonergic axons.Neurorehabilitation & Neural Repair. 14(4):311–7, 2000.

[66] Grill R.J., A. Blesch and M.H. Tuszynski (1997). Robust growth of chronically injured spinal cord axons induced by grafts of genetically modified NGF-secreting cells. Exper. Neurol. 148:44–452.

[67] Lu K.W., Chen Z.Y., Jin D.D., Hou T.S., Cao L., Fu Q. Cationic liposome-mediated GDNF gene transfer after spinal cord injury. Journal of Neurotrauma. 19(9):1081–90, 2002.

sion.[68] NT–3 gene in an adenoviral vector was delivered to the spinal motoneurons by retrograde transport through the sciatic nerve, causing induced growth of axons from the intact corticospinal tract across the midline to the denervated side.[69] Another approach is to actually stimulate one of the intracellular pathways that play a role in neurite outgrowth. Viral delivery of vectors carrying the mutated form of MEK1 that activates of the extracellular-signal-regulated kinases (ERKs) induces axonal regeneration across the transection site of the spinal cord in young rats.[70] Newer approaches that direct transient production of growth factors specifically in motor neurons also hold great promise.[71]

Substrate or Matrix: There have been several studies that provide a substrate for growth is useful. Self-assembling peptide scaffolds support differentiation as well as extensive neurite outgrowth in culture.[72] When a collagen tube is implanted into hemisected adult rat spinal cord, there is growth of the rostral spinal axons into the caudal ventral roots.[73] Growth factor-treated nitrocellulose implants that bridge a complete transection lesion of adult rat spinal cord caused regrowth of ascending sensory axons across the traumatic spinal cord injury site.[74] Implants using poly-beta-hydroxybutyrate (PHB) as carrier scaffold and containing alginate hydrogel, fibronectin, and Schwann cells can support neuronal survival and regeneration after spinal cord injury.[75] Using a polymer scaffold seeded with stem cells led to better functional recovery in hemisected SC and appeared to encourage the growth of corticospinal axons.[76] When a hydrogel is implanted into the injury site of a rat with chronic, severe SCI, there was improved function and evidence of blood vessels, and axonal growth.[77]

Modifying the Immune System: The immune system plays an important role in spinal cord injury. Many cytokines and other factors released by immune cells also influence neural cells. Several studies suggest a benefit of activated macrophages or specific T cells in reducing the amount of secondary injury and stimulating growth after spinal cord injury in rats.[78] Recent clinical trials using activated macrophages are being conducted in Israel.[79] However, others have found that activation of macrophages in a normal cord can actually cause axonal injury and demyelination[80] and suggests inherent danger of activating the immune system

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[68] Sakamoto K., Uvelius B., Khan T., Damaser M.S. Preliminary study of a genetically engineered spinal cord implant on urinary bladder after experimental spinal cord injury in rats. Journal of Rehabilitation Research & Development. 39(3):347–57, 2002.

[69] Zhou L., Baumgartner B.J., Hill-Felberg S.J., McGowen L.R., Shine H.D. Neurotrophin-3 expressed in situ induces axonal plasticity in the adult injured spinal cord.Journal of Neuroscience. 23(4):1424–31, 2003.

[70] Miura T., Tanaka S., Seichi A., Arai M., Goto T., Katagiri H., Asano T., Oda H., Nakamura K. Partial functional recovery of paraplegic rat by adenovirus-mediated gene delivery of constitutively active MEK1.Experimental Neurology. 166(1):115–26, 2000.

[71] Jackson, C.A., C. Cobbs, J.D. Peduzzi, M. Novak and C.D. Morrow (2001) Repetitive Intrathecal injections of Poliovirus Replicons result in gene expression in neurons of the central nervous system without pathogenesis. Human Gene Therapy, 12:1827–1842.

[72] Holmes T.C., de Lacalle S., Su X., Liu G., Rich A., Zhang S. (2000) Extensive neurite outgrowth and active synapse formation on self-assembling peptide scaffolds. PNAS 97:6728–33.

[73] Liu S., Said G., Tadie M. Regrowth of the rostral spinal axons into the caudal ventral roots through a collagen tube implanted into hemisected adult rat spinal cord. Neurosurg. 49:143–50, 2001.

[74] Houle J.D. and M.K. Ziegler (1994) Bridging a complete transection lesion of adult rat spinal cord with growth factor-treated nitrocellulose implants. J. Neural Transplant. & Plast. 5:1115–124.

[75] Novikov L.N., Novikova L.N., Mosahebi A., Wiberg M., Terenghi G., Kellerth J.O. A novel biodegradable implant for neuronal rescue and regeneration after spinal cord injury. Biomaterials. 23(16):3369–76, 2002.

[76] Teng Y.D., Lavik E.B., Qu X.. Park K.I., Ourednik J., Zurakowski D., Langer R., Snyder E.Y. Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells. Proceedings of the National Academy of Sciences of the United States of America. 99(5):3024–9, 20.

[77] Woerly S., Doan V.D., Evans-Martin F., Paramore C.G., Peduzzi J.D. Spinal cord reconstruction using NeuroGel implants and functional recovery after chronic injury.Journal of Neuroscience Research. 66(6):1187–97, 2001.

[78] Hauben E., Agranov E., Gothilf A., Nevo U., Cohen A., Smirnov I., Steinman L., Schwartz M. Posttraumatic therapeutic vaccination with modified myelin self-antigen prevents complete paralysis while avoiding autoimmune disease. Journal of Clinical Investigation. 108(4):591–9, 2001.

[79] *http://www.biospace.com/company__profile.cfm?CompanyID=4350*

[80] Popovich P.G., Guan Z., McGaughy V., Fisher L., Hickey W.F., Basso D.M. The neuropathological and behavioral consequences of intraspinal microglial/macrophage activation. Journal of Neuropathology & Experimental Neurology. 61(7): 623–33, 2002.

after SCI.[81] IL–10 is neuroprotective after a spinal cord injury.[82] Another study found that IL–10 and MPS reduce the amount of damaged tissue but do not change functional outcome.[83]

Inhibitors and Scar: For many years, Schwab and colleagues explored the potential of the IN–1 antibody to block myelin associated inhibitory molecule, Nogo, after SCI. IN–1 caused improvement in function if given shortly after injury.[84] Other myelin-associated inhibitors such as MAG have been described. Blockers of Nogo and MAG appear to cause functional improvement.[85] Many suggest that the scar inhibits[86] and have tried various inhibitors such as iron chelators.[87] Beta-aminopropionitrile treatment that inhibits the formation of glial scar accelerates recovery of mice after spinal cord injury.[88] Other efforts involve implantation of a collagen tube to interfere with scar formation.[89] The semaphorins may be important contributor to the inhibitory effects of the scar.[90]

Rehabilitation: There has been tremendous progress in the field of rehabilitation with use of weight-supported treadmills,[91] functional electrical stimulation and biofeedback. In our own lab, we found a statistically significant improvement in rats with a moderate degree of spinal cord injury that are placed in an enriched environment compared to standard caging.[92] An enriched environment consists of a social environment where there is free access to novel items that include exercise equipment.

My primary reason for being here today is that I don't want victims of injuries and diseases to again become victims. The best chance of cellular treatment for them is using their own stem cells. Victims of injuries and diseases are again being used to justify a treatment that is not in their best interest. Both the clinical trials and pre-clinical trials suggest that adult stem cells and/or using one's own stem cells is a more effective treatment for diseases and injuries. The data just keep accumulating that this is the direction to go despite the fact that most of the research is being done using embryonic stem cells in experimental animals or human cell lines.[93] The least funded area is still 'bench to bedside' research using one's own stem cells or using adult stem cells. Despite the fact that there are much fewer experimental studies using adult stem cells, amazing progress has been made as evidenced by the clinical trials. The idea that we should look to cloning for a treatment for diseases or injuries is way in the future. Despite all the claims of its promise there has been only 1 or 2 experimental animal study to suggest that this is a prom-

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[81] Jones T.B., Basso D.M., Sodhi A., Pan J.Z., Hart R.P., MacCallum R.C., Lee S., Whitacre C.C., Popovich P.G. Pathological CNS autoimmune disease triggered by traumatic spinal cord injury: implications for autoimmune vaccine therapy. Journal of Neuroscience. 22(7):2690–700, 2002.

[82] Bethea J.R., Nagashima H., Acosta M.C., Briceno C., Gomez F., Marcillo A.E., Loor K., Green J., Dietrich W.D. Systemically administered interleukin-10 reduces tumor necrosis factor-alpha production and significantly improves functional recovery following traumatic spinal cord injury in rats. [Journal Article] Journal of Neurotrauma. 16(10):851–63, 1999.

[83] Takami T., Oudega M., Bethea J.R., Wood P.M., Kleitman N., Bunge M.B. Methylprednisolone and interleukin-10 reduce gray matter damage in the contused Fischer rat thoracic spinal cord but do not improve functional outcome. Journal of Neurotrauma. 19(5):653–66, 2002.

[84] Merkler D., Metz G.A., Raineteau O., Dietz V., Schwab M.E. Fouad K.Locomotor recovery in spinal cord-injured rats treated with an antibody neutralizing the myelin-associated neurite growth inhibitor Nogo-A.Journal of Neuroscience. 21(10):3665–73, 2001.

[85] GrandPre T., Li S., Strittmatter S.M. Nogo-66 receptor antagonist peptide promotes axonal regeneration. Nature. 417(6888): 547–51, 2002.

[86] Hermanns S., Klapka N., Muller H.W. The collagenous lesion scar—an obstacle for axonal regeneration in brain and spinal cord injury.Restorative Neurology & Neuroscience. 19(1–2):139–48, 2001.

[87] Hermanns S., Reiprich P., Muller H.W. A reliable method to reduce collagen scar formation in the lesioned rat spinal cord.Journal of Neuroscience Methods. 110(1–2):141–6, 2001.

[88] Gilad G.M., Gilad V.H. Beta-aminopropionitrile treatment can accelerate recovery of mice after spinal cord injury.European Journal of Pharmacology. 430(1):69–72, 2001.

[89] Spilker M.H., Yannas I.V., Kostyk S.K., Norregaard T.V., Hsu H.P., Spector M. The effects of tubulation on healing and scar formation after transection of the adult rat spinal cord. Restorative Neurology & Neuroscience. 18(1):23–38, 2001.

[90] Pasterkamp R.J., Anderson P.N., Verhaagen J. Peripheral nerve injury fails to induce growth of lesioned ascending dorsal column axons into spinal cord scar tissue expressing the axon repellent Semaphorin3A.European Journal of Neuroscience. 13(3):457–71, 2001.

[91] 6. Edgerton V.R., Roy R.R., Hodgson J.A., Prober R.J., de Guzman C.P., de Leon R. Potential of adult mammalian lumbosacral spinal cord to execute and acquire improved locomotion in the absence of supraspinal input. J. Neurotrauma. 9 Suppl 1:S119–28, 1992.

[92] Fischer, F.R. and J.D. Peduzzi. Functional improvement in rats with chronic spinal cord injuries after exposure to an enriched environment. Soc. Neurosci. Abstr., 23:2188, 1997.

[93] Neil Munro. SCIENCE: Petri-Dish Politics. National Journal, 04–19–2003.

ising direction.[94] We have at least 200 experimental animal studies in the field of spinal cord injury alone that show that a particular cellular, growth factor, or other treatment causes a functional or anatomical improvement and only 1 or 2 in the field of cloning despite the fact that there is no ban on performing animal cloning. With only a limited amount of funding available, more focus is needed in directing research funds to areas that can help people in the next 5–10 years and not several lifetimes away.

Senator BROWNBACK. Thank you, Dr. Peduzzi.

We have a vote on. First, I want to announce that I'll be joining other Members in a letter to promote and push for the funding for a national cord-blood bank system and the funding that you were talking about, Dr. Kurtzberg, that's going to be needed to do this. I know Senator Hatch is going to be joining in this letter, and I think we'll have several others. And we'll also be helping with legislation on a national cord-blood banking program. I think this has extraordinary opportunities, and I really applaud your work and Dr. Rubinstein's work that you're doing in this field that really holds so much promise. It's beautiful, beautiful work. And we'll be pushing for that to see if we can't get that mature on forward.

This is very interesting to see and to hear, and exciting. I appreciate all of your passions and your help and your work that each of you are doing in this field.

We've got a vote on that I'm going to move over for. And then what I think we'll do is, we'll bring the next panel up while I recess this for a period of time, and then bring that next panel up.

But I hope, in the next year-and-a-half, we make as much progress as we made in the past year-and-a-half. I think you will see a fascinating array of people being treated and helped if we're able to put in the resources here, if we're able to really move forward in these fields of regenerative medicine. The adult work, the cord blood, has been beautiful in its successes and are really exciting to see these moving forward.

We will be in recess for approximately 15 minutes. If I could have the next panel ready to go when I get back, and then we'll move forward.

Thank the panelists for being here today.

We're in recess for 15 minutes.

[Recess.]

Senator BROWNBACK. Call the hearing back to order.

I want to apologize for making it over and back so fast, I didn't have as much time to spend with those who wanted to visit with me.

We've got an exciting next panel that I would like to call up. And the last panel was very informative, as well. These are patients, who have been working on and been involved in some really incredible things. Mr. Steven L. Barsh, from Pennsylvania; Mr. Keone Penn, from Snellville, Georgia; and Mr. Stephen R. Sprague, from Staten Island, New York, the people that will be testifying, and we look forward to hearing your comments and the testimony.

I would say to each of you, we have your written testimony in the record, so you can summarize, if you'd like or you can go all go off this testimony, whichever you would like, or you can submit

[94] Rideout W.M. III, Hochedlinger K., Kyba M., Daley Q. and Jaenisch R. Correction of a genetic defect by nuclear transplantation and combined cell and gene therapy Cell 109:17–27.

your written testimony for the record and then say what you please here. And then I look forward to being able to question each of you for a little bit, if possible.

I thank you all very much for coming here, appreciate your being willing to attend. And, Ms. Penn, I appreciate you being willing to come, accompanying your son, here today, as well. Mr. Barsh, delighted to have you.

STATEMENT OF STEVEN L. BARSH,
MERION STATION, PENNSYLVANIA

Mr. BARSH. Thank you, Senator Brownback. And, by the way, do we have 5 minutes or 7 minutes for our testimony?

Senator BROWNBACK. I'm going to run the clock at 7 minutes, just to give you some guidance.

Mr. BARSH. No problem.

Senator BROWNBACK. As you can see, it's not a hard and fast rule, but it gives you a little bit of guidance.

Mr. BARSH. It's greatly appreciated. Unfortunately I'm not a patient; I'm a parent. Our son, Spencer, couldn't be here today. He's three and a half. It was too much for him to come down from Philadelphia, and he had some therapy this morning. So I'm just the parent of a patient. But good afternoon.

Thank you for the opportunity to testify today on the very important topic of cord blood, and why a national cord-blood stem cell bank network should be provided for to save the lives of some of this great nation's most severely ill children and adults.

We first learned, a little over 2 years ago, that our one-year-old son, Spencer, had ALD, or adrenoleukodystrophy. In 50 percent of ALD children, more and more of their brains vanish due to this rare neurodegenerative disease, leading to loss of function and death by age ten. The remaining 50 percent have a severe-to-deadly form as adults. A parent's worst nightmare, or, in this case, a day-mare, because you actually have to live through it. This is the disease behind the film, Lorenzo's Oil, if you're familiar with that film. As a matter of fact, Lorenzo's father is in this room today, a very great man.

Senator BROWNBACK. Would he care to stand so we could recognize him?

Mr. BARSH. Oh, he's just stepped out. Augusto Odone. I'm sorry.

Senator BROWNBACK. Well, we'll try to recognize him when he comes back.

Mr. BARSH. I apologize. He is present today. A very great man.

Spencer, our son, started to have repeated MRI brain studies. In February of last year, these MRI studies showed changes had started in his brain, indicating that the deadly brain deterioration had begun.

Cord-blood and bone-marrow transplants are the only accepted therapies when this ALD brain deterioration begins and is caught in time, as Dr. Kurtzberg referenced. You need to catch these diseases in time.

Via the National Marrow Donor Program, or the NMDP, we searched for a perfect six-out-of-six bone-marrow match, and couldn't find one. And, as some of the doctors or researchers alluded to earlier, finding a good match is really important. Other-

wise, particularly in bone marrow, it doesn't work real well and it has a pretty poor outcome, to put it mildly. Plus, we were looking at nearly 6 months before we could even get Spencer to transplant, while his brain would continue to break down and deteriorate, because going the bone-marrow route takes a lot of time.

See, even if you find someone on the National Marrow Donor Program donor list, it doesn't mean you can get to them quickly. It's a heartbreaking and gut-wrenching process of calling in potential donors that they identify through their network, having them screened, confirming that they'll go through surgery to remove some of their bone marrow, et cetera. You lose precious time waiting. And in these neurodegenerative diseases, it's a time issue. You really need to transplant very, very quickly. Worse yet, more than 50 percent of people are turned away by the NMDP, told there's no suitable donor for them. So about, you know, 50 to 60 of every 100 people that knock on their door looking for a solution are told, "Sorry, we can't help you."

ALD, like many metabolic diseases, can move very quickly along its destructive path, and horrifying changes can often be seen daily in your child. This is particularly true for rare metabolic diseases discussed earlier, such as Hurlers, MLD, or metachromatic leukodystrophy, Tay-Sachs, and others—all diseases that can now be treated by a cord-blood transplant.

In metabolic diseases, lessening the time to transplant equals less deficits and a better transplant outcome. As discussed, time is enemy number one. And, in cord blood, the unit has already been typed, checked, prepped, and is waiting in a freezer right now. There just needs to be more of it.

Spencer's pre-transplant work-up testing started just 4 weeks after we found a bad MRI of his brain, and only 5 days after my wife and I made the decision that he should be transplanted. There was no 6 months of waiting. We held on tightly to our two-and-a-half-year-old son, Spencer, while he was in a pediatric isolation and intensive-care unit for nearly 40 days. There, he received his cord-blood stem cell transplant, preceded by highly toxic medications, including massive, massive chemotherapy. He was lucky. He had what's been considered and characterized an "easy course of transplant."

At the same time, we saw kids who didn't make it, as the procedure proved too toxic. While core-blood stem cells work for most of their very, very fortunate recipients, more research needs to be done. More and higher-quality cord-blood units need to be available, not only for transplantation, but for research purposes. And stem cell research, in general, needs to be carefully and properly further explored to harness all of its life-saving potential. Those greater units and greater research, particularly in cord blood, would come about by passage of this bill.

Spencer's cord-blood transplant was just 14 months ago. But who's counting? He's doing extremely well. As a matter of fact, I'm happy to say he starts summer camp in 2 weeks. It'll be his first time he ever goes to camp, school, nursery school, anything, in his entire life. And he'll walk into that camp as a normal little boy.

We see improvements and problem reversal on a weekly basis. At only 6 months post-transplant, physicians began to see improve-

ments in Spencer's brain MRI, as well as his clinical presentation. It appears that Spencer is actually re-myelinating, meaning that the cord-blood stem cells are repairing his brain. The early progenitor stem cells from the cord blood are differentiating into other cell types.

The MRI and clinical observations have been confirmed both at Duke and by a diverse team at Children's Hospital of Philadelphia, or CHOP. I believe the non-technical word they have used is "amazing," going on to say, "We've never seen anything like this. We don't usually see brain MRIs improve."

Cord blood works. With only one-tenth of the funding provided to the National Marrow Donor Program today, cord blood from a national cord-blood stem cell bank network is a solution for more than the 50 percent of people who the NMDP turns away. These treatment options must be available to the children and adults who have these devastating diseases, including malignant diseases, such as leukemias.

In closing, it's important to remember that you can get to transplant with cord blood extremely quickly, which is very, very critical with many diseases. The early progenitor stem cells in Spencer now appear to be differentiating into other cell types and are repairing problems in his brain. "Just amazing" is the term we hear time and again.

At only one-tenth of the funding provided to the NMDP, a national cord-blood stem cell bank network can be provided so that this life-saving technology, that works today, can be available to everyone in need.

We now have a normal and healthy 3-year-old son. His name is Spencer Barsh. And cord blood saved his life.

Thank you for your time and thoughtful consideration on this matter.

[The prepared statement of Mr. Barsh follows:]

PREPARED STATEMENT OF STEVEN L. BARSH, MERION STATION, PENNSYLVANIA

Good afternoon.

Thank you for the opportunity to testify today on the very important topic of cord blood and why a National Cord Blood Stem Cell Bank Network should be provided for to save the lives of some of this great nation's most severely ill children and adults.

We first learned a little over 2 years ago that our one year old son Spencer had ALD or Adrenoleukodystrophy. Fifty percent of ALD children have a deadly cerebral onset of this rare neurodegenerative disease leading to loss of function and death by age 10. The remaining 50 percent have a severe to deadly form as adults. A parent's worst nightmare, this is the disease behind the film *Lorenzo's Oil*.

Spencer started to have repeated MRI brain studies and in February of last year, MRI studies showed changes had started in his brain indicating a deadly cerebral onset had begun.

Cord blood and bone marrow transplants are the only "accepted" therapies when a cerebral onset of ALD has begun and is caught in time.

Via the National Marrow Donor Program (NMDP) we had already been searching for a perfect 6/6 bone marrow match and couldn't find one. Plus, we were looking at nearly 6 months before we could even get to transplant while Spencer would be deteriorating.

Even if you find someone on the NMDP donor list, it doesn't mean you can get to them quickly. It's a heartbreaking and gut-wrenching process of calling in *potential* donors, having them screened, confirming they will go through surgery, etc. You lose precious time, waiting. Worse yet, more than 50 percent of people are turned away told there is no suitable donor for them.

ALD, like *many* metabolic diseases, can move very quickly along its destructive path and deficit changes can sometimes be seen daily. This is particularly true for rare metabolic diseases such as Hurler's, MLD, Tay-Sachs, and others—all diseases that can now be treated by a cord blood transplant.

In metabolic diseases, lessening the time to transplant equals less deficits and a better transplant outcome. Time is enemy #1. In cord blood, the unit has already been typed, checked, prepped, and is *waiting* in a freezer *right now.*

Spencer's pre-transplant work-up testing started just *4 weeks* after his bad MRI (only *5 days* after my wife and I made the decision that he should be transplanted). There was no 6 months of waiting.

We held on tightly to our 2½-year-old son Spencer while he was in a pediatric isolation and intensive care unit for nearly 40 days. There he received his cord blood stem cell transplant preceded by highly toxic medications including massive chemotherapy. He was lucky. He had what was considered an "easy course of transplant."

At the same time, we saw kids who didn't make it as the procedure proved too toxic. While cord blood stem cells work for most of their very fortunate recipients, more research needs to be done. More and higher quality cord blood units need to be available not only for transplantation, but for research purposes; and stem cell research in general needs to be carefully and properly further explored to harness all of its life saving potential.

His cord blood transplant was just 13 months ago, but who's counting?

He is doing extremely well.

We see improvements and *deficit reversal* on a weekly basis. At only 6 months post transplant, *physicians* began to see *improvements* in Spencer's MRIs as well as clinical presentation.

It appears that Spencer is actually re-myelinating as the early progenitor stems cells from the cord blood are *differentiating* into other cells types in his brain.

The MRI and clinical observations have been confirmed both at Duke and by a diverse team at the Children's Hospital of Philadelphia (CHOP). I believe that the non-technical word they have used was "amazing" going on to say "They've never seen anything like this. We usually don't see MRIs improve."

Cord blood works.

With only 1/10 of the funding provided to the NMDP today, cord blood from a National Cord Blood Stem Cell Bank Network is a solution for the more than 50 percent of people who the NMDP turns away.

These treatment options must be available to the children and adults who have these devastating diseases including malignant diseases.

In closing:

- It's important to remember that you can get to transplant with cord blood extremely quickly which is very, very critical with many diseases.
- The early progenitor stem cells in Spencer now appear to be differentiating into other cell types that are repairing problems in his brain. "Just amazing" is the term we hear time and again.
- At only 1/10th of the funding provided to the NMDP, A National Cord Blood Stem Cell Bank Network can be provided for so that this life saving technology, that works today, can be available to everyone in need.

We now have a normal 3 year old son.

His name is Spencer Barsh.

Cord blood, saved his life.

Thank you for your time and thoughtful consideration.

Senator BROWNBACK. Thank you for being here, Mr. Barsh. You know, when you talk about him going to summer camp, you amaze at the simple pleasures and what they truly mean. That's a beautiful story.

Mr. BARSH. We cherish every day.

Senator BROWNBACK. Mr. Sprague, thank you very much for joining us here today, and I would turn to you next.

STATEMENT OF STEPHEN R. SPRAGUE,
STATEN ISLAND, NEW YORK

Mr. SPRAGUE. Thank you, Senator.

I certainly am personally fortunate to have an opportunity to speak with you today; not in medical terms, but from a patient's perspective. I know you can't tell, but you're looking at an aging baby-boomer. And I was already a medical veteran before I got my leukemia diagnosis. That was 7 years ago. I was 47 years old. I was a diabetic. I had survived a heart attack and bypass surgery, all in 1993. In spite of all that medical training, I was totally unprepared for a battle with cancer.

This was in November 1995. In those days, chemotherapy only stalled the inevitable for long-term survival, and that was, of course, the traditional bone-marrow transplant. "The cure that can kill," we like to call it.

Although CML, which was my diagnosis, usually progresses slowly, in May 1997, only 18 months after my initial diagnosis, I found myself in blast crisis, the end-stage of the disease.

Meanwhile, my oncologist began what would quickly become a very frustrating marrow-donor search. I soon discovered that less than a third of those seeking transplant have a matching sibling, the best and most obvious donor source. I was an only child. I needed to find an unrelated donor if a transplant were even to be an option for me.

To make a very long story short, I was not one of the lucky ones to find a match in any of the marrow-donor registries. "Enjoy your remission for as long as you can. Get your affairs in order," I remember them telling me, "while we keep looking and try to figure something else out."

This sad predicament is still all too familiar for many adult leukemians. Even now, far too many patients are unable to proceed to transplant due to the complexity, as you've heard already earlier—the complexity of antigen matching, as well as the problems inherent in tracking down, collecting the matching marrow from a hopefully still willing and still available marrow donor.

Fortunately, as I was, unfortunately, beginning to lose my remission, my doctor was planning to begin one of the very first clinical trials for end-stage adult CML'ers using neonatal stem cells, those from cord blood. A perfect cord-blood match was found for me within days, from the New York Blood Center's world-renowned Placental Blood Program, as it was known back at that time. And in life-or-death struggles like these, days do matter.

Incredibly, some still anonymous New York City mother had decided to do what few mothers were doing back then, and that was to donate her newborn cord blood to a public cord-blood bank. It was that donation, from that newborn baby girl, that just happened to be my one and my only stem cell match.

I entered the hospital October 30, 1997. Magic and miracles happened. And, by the grace of God, I was discharged 40 treacherous days later, but with a new, working immune system, no trace of leukemia. And no hair.

[Laughter.]

Mr. SPRAGUE. Here I am today, 5 years, 7 months, and 12 days later—and, believe me, I count every one of them—with a 100 per-

cent donor cells, all female chromosomes, just like my donor, completely cancer free. Still not much hair.

[Laughter.]

Mr. SPRAGUE. In my post-transplant years as a patient advocate, I've come to learn a lot of things—about myself, about life and death, about perspectives, about appreciations and priorities, but, most importantly, about hope. Part of that hope, for desperate patients seeking transplant, patients like I was, involves options. Heading down the transplant trail is a risky endeavor, even in the best of circumstances, but that critical first step can't ever be taken without first finding the right stem cell match. Cord blood remains a largely untapped, non-controversial, readily available alternative source of non-embryonic stem cells.

That's the good news. That most of it continues to be trashed as medical waste instead of finding its way into a public cord-blood bank, that remains the problem. But it's a solvable problem, as you've heard.

Registering the good intentions of prospective volunteer marrow donors has been one solution to providing stem cells to patients in need. Collecting and preserving the actual cord blood, thanks to new parents who are willing, who are eager, to donate at the time of delivery, may be a better solution, or at least a viable option.

As cord blood finds its way into the medical mainstream, it's my personal hope, shared by my cancer companions—the lucky ones like me, as well as the less fortunate ones, who have died waiting while searching for their elusive marrow match—that an infrastructure to assist patients nationwide can be created, regulated, funded to take better advantage of this natural and precious gift of life.

If more of those estimated 4 million new parents each year have a better opportunity to donate their newborn's cord blood, an important new donor bank can be created quickly, conveniently, without pain and without controversy. And it certainly remains my privilege to serve as living proof of the promise of cord blood for the adult leukemia community.

You know, we think of leukemia as a children's disease, but 90 percent of all leukemia cases are diagnosed in middle-aged adults, like me, like some of you. Regardless of age, cord blood is a proven alternative for saving lives, that needs your support to become more readily available.

Again, I thank you for the privilege of telling my story and sharing my concerns.

[The prepared statement of Mr. Sprague follows:]

PREPARED STATEMENT OF STEPHEN R. SPRAGUE, CORD BLOOD CRUSADER, STATEN ISLAND, NEW YORK

Mr. Chairman and Members of the Subcommittee:

My name is Stephen Sprague and I am personally fortunate to have the opportunity of speaking with you today. In a life before leukemia, I've appeared before lots of committees, but never about matters affecting life or death. Today, I'm here wearing a proud new hat . . . that of a long-term adult cord blood transplant survivor, and my remarks are much more critical . . . for those like me in the cancer community, and I hope, for you who have an opportunity to help us now . . . not with more research, but by supporting proven patient applications.

While you probably can't tell, I'm an aging baby boomer and was already a medical veteran before I got my leukemia diagnosis 7 years ago at age 47. I'm a diabetic and had survived a heart attack and quadruple bypass surgery in 1993. In spite of that, I was totally unprepared for a battle with cancer. This was November 1995. In those days, and even today with new experimental wonder drugs for cancer, chemotherapy only stalled what was inevitable for long-term survival. . .the traditional bone marrow transplant. "The Cure That Can Kill" as some of us have learned to call it. Since CML is usually a slowly-progressing, manageable cancer, I continued to seek a decent quality-of-life while mentally preparing for transplant . . . the only option. For whatever reason, in May 1997, only 18 months after my initial diagnosis, I found myself in blast crisis, the end-stage of this disease.

After a rigorous few months in the hospital, my oncologist, Dr. Andrew Pecora, got me into my first remission while we began what would quickly become a frustrating marrow donor search. I soon discovered that less than a third of those seeking transplant have a matching sibling, the best and most obvious donor source. Since I was an only child, I needed to find an unrelated matching donor if a transplant were to even be an option for me. To make a very long and complicated story short, I was *not* one of the lucky ones to find an acceptable match in any of the marrow donor registries. *"Enjoy your remission for as long as you can and get your affairs in order"* I was told, *"while we keep looking and try to figure something else out."*

This sad predicament is still an all-too-familiar one for many adult leukemians. Even now, far too many patients referred for a primary marrow donor search are unable to actually proceed to transplant due to the complexity of antigen matching, as well as the problems inherent in tracking down and eventually collecting the matching marrow from a hopefully still-willing and still-available donor. Fortunately for me, there soon came a series of events that, to this day, I find difficult to understand or describe.

Just as I was beginning to lose my remission, my doctor, who directs Hackensack (NJ) University Medical Center's prestigious Stem Cell Transplant Program, was planning to begin one of the very first clinical trials for end-stage adult CMLers using neonatal stem cells obtained from umbilical cord blood. And equally astonishing, a perfect cord blood match was found for me within days, from the New York Blood Center's world-renowned Placental Blood Program, as it was known at the time. And in life-or-death struggles like these, days matter. Incredibly, some still-anonymous New York City mother had decided to do what few new mothers were doing back in those days . . . donating their newborn's cord blood to a public cord blood bank. It was that donation from a newborn baby girl that happened to be my one and only match.

I entered the hospital on October 30, 1997. Magic and miracles happened, including a pioneering treatment using cord blood. And by the grace of God, I was discharged 40 treacherous days later, December 8, 1997, with a new, working immune system and no trace of leukemia. And no hair. Fast-forward a bit and here I am today . . . 5 years, 7 months and 12 days later . . . with 100 percent donor cells, all-female chromosomes just like my donor, completely cancer-free and in relatively good health. And still not much hair.

In my post-transplant activities as a patient advocate volunteer, I have come to learn a lot of things. . .about myself, about life and death, and about perspectives, appreciations and priorities. And most importantly, about hope.

My point is simply this. Part of that hope for desperate patients seeking transplant . . . patients like I was . . . involves options. Heading down the transplant trail is a risky endeavor, even in the best of circumstances. But that critical first step can't ever be taken without first finding the right stem cell match.

As you will come to appreciate, umbilical cord blood remains a largely untapped, non-controversial and readily available alternative source of non-embryonic, neonatal stem cells. That's the good news. That most of it continues to be trashed as medical waste instead of finding its way into a public cord blood bank remains the problem. A solvable problem. Registering the good intentions of prospective volunteer marrow donors has been one solution to providing stem cells to patients in need. Collecting and preserving the actual cord blood thanks to new parents willing and eager to donate at the time of delivery may be a better one. Or at least another viable option.

As cord blood finds its way into the medical mainstream, it is my personal hope, shared by my cancer companions . . . the lucky ones as well as the less fortunate ones who have died searching for their elusive marrow match . . . that an infrastructure to assist patients nationwide can be created, regulated and funded to take better advantage of this natural and precious "gift of life." If more of those estimated 4 million new parents each year have a better opportunity to donate their

newborn's cord blood, an important new donor bank can be created quickly, conveniently, without pain, and without controversy. And it remains my privilege to serve as living proof of the promise of cord blood for the adult leukemia community. Although we think of it as a children's disease, 90 percent of all leukemia cases are diagnosed in middle-aged adults. But regardless of age, cord blood is a proven alternative for saving lives that needs your support to become more readily available.

Thank you for the opportunity to share my concerns with you and I would be happy to answer questions at the appropriate time.

STEPHEN R. SPRAGUE,
Cord Blood Crusader.

Senator BROWNBACK. And thank you. What an encouraging story.

Have you done any public-service announcements? Because you've got a natural gift here.

[Laughter.]

Mr. SPRAGUE. Oh, thank you, Senator. In a former life, life before leukemia, I appeared before lots of committees, but never on something about life or death. It was always about all the unimportant stuff. So I appreciate this opportunity.

Senator BROWNBACK. We spend a lot of time on unimportant stuff. But we do spend some time on important things, as well. And you're sitting next to quite a star.

Mr. Penn, you've received quite notoriety, I know, already, you're quite a remarkable young man. Will you tell us your story?

STATEMENT OF KEONE PENN, SNELLVILLE, GEORGIA

Mr. PENN. My name is Keone Penn. Two days ago, I turned 17. Five years ago, they said I wouldn't live to be 17.

I was born with sickle-cell anemia. My mother said I was a crying baby. She didn't realize I was in pain.

I had a stroke when I was 5 years old. The teacher called my mom from preschool and said that I had been acting funny all day. My mother knew the symptoms, because she had seen it with my grandparents.

They had to do a blood exchange of my whole body. I had brain damage to the right side of my brain. I couldn't walk or talk for a long time. I had to relearn everything.

Things got worse after that. My life was full of pain crises, blood transfusions, and more times in the hospital than I can count. I was never able to have a normal life. I couldn't play sports, like basketball or football.

And I had a tube in my chest, and some kids bullied me and threatened to hit me in my chest, and I felt like an outsider, like I wasn't a normal kid. And it was just hard.

And I was suicidal then. Every day I'd go to school and people would pick on me. I couldn't take it any more. One day, I came home from school with a sad look on my face. My sister got home after me, and my mom had went to work. I went in my room, sat on my bed, and cried. I had suicide on my mind.

Then I thought about my family, how they would miss me. I thought about my mom, my sister, my aunt, and my cousin, how they would cry if I, you know, would die. I held my head up and dried my eyes. My mother always said we have to do what we have to do, and that you have to deal with the life you are given.

The year before I had the transplant, I was in the hospital 13 times. I knew everybody in the hospital and had been in just about every room on the floor.

Then my mom, one day when I was in the hospital, she came into the room, looking all depressed, because I had had a pain crisis. And she was really sad, and she just looked at me, and said, "Keone, they want to try something. They want to do a cord-blood transplant. They said if you don't do it in the next 5 years, you're going to have another stroke that could be fatal. And this is experimental, and, you know, we have to work together on this." And she said, "So what do you think? Do you want to do it?" And I was thinking I'd rather go out fighting than just wait and know you're going to die, you know, because nobody wants to die. So I said yes, and we did the cord-blood transplant.

My cord-blood transplant wasn't easy, but I thank God I'm still here. I had a lot of problems, like graft versus host disease, which is a rejection of the new cells.

I thought the coolest part about my transplant was that my blood type has changed from O to B.

[Laughter.]

Mr. PENN. I missed a lot of school, and I had to do a couple of years of home-schooling. But I still made all A's and B's. I made B's this year.

[Laughter.]

Mr. PENN. Next year, I will graduate from high school. My family will be so proud to see me graduate, because they thought I wouldn't live long enough to graduate. Before I had my transplant, they said I wouldn't live another 5 years.

My graduation will mark a big victory in my life. I want to become a chef. I plan to go to a good culinary arts school in Georgia. I cook for my family all the time. I think I'm pretty good at it.

[Laughter.]

Mr. PENN. My life, with sickle cell, was very rough. I have been through more things than most grownups can only imagine. But sickle cell is a part of my past. One year after my transplant, they pronounced me cured of sickle-cell anemia. Cord blood saved my life. Now I can look forward to a brighter future.

Thank you.

[The prepared statement of Mr. Penn follows:]

PREPARED STATEMENT OF KEONE PENN, SNELLVILLE, GEORGIA

My name is Keone Penn. Two days ago, I turned 17 years old. Five years ago, they said I wouldn't live to be 17. They said I'd be dead within 5 years. I was born with sickle cell anemia. Sickle cell is a very bad disease. I had a stroke when I was 5 years old. Things got even worse after that. My life has been full of pain crises, blood transfusions every two weeks, and more times in the hospital than I can count. The year before I had my stem cell transplant, I was in the hospital 13 times. I never was able to have a normal life. My stem cell transplant was not easy, but I thank God that I'm still here. I will graduate from high school this year. I want to become a chef because I love to cook. I think I'm pretty good at it. Sickle cell is now a part of my past. One year after my transplant, I was pronounced cured. Stem cells saved my life. Thank you.

Senator BROWNBACK. Thank you.

Those are very impressive statements and very impressive comments.

Mr. Barsh and Mr. Sprague, I'm curious—and you may want to involve any of the researchers that can comment on this, as well.

Senator BROWNBACK. You have commented that timing is critical determining the need for cord blood. Every minute, every day counts on this.

Mr. Barsh, you were right on top of this at an early phase. How do we catch these earlier? What's your advice on how we catch these to be able to intercept as fast as possible, number one? And I want to ask you, as well, is this the sort of thing if you catch it right at birth, you're likelihood of success is far greater than if it drags on for a period of time?

Mr. BARSH. Senator, they're all excellent questions, and thank you for asking me, and I'll just comment.

One way that these types—or many, but not all—of the neurodegenerative diseases can be caught is by better prenatal testing—or testing, immediately after birth, like PKU testing, which is mandated today for every baby born. It's done on a state-by-state basis, but not a Federal basis. In about a year, there's going to be a test for adrenoleukodystrophy, so it could be screened and caught earlier.

Ours was caught in a very unfortunate circumstance, where one of Spencer's oldest cousins is in a persistent vegetative state from ALD today. There were three boys in our family that had it, because it's X-linked and gets passed down. So Oliver was the martyr and won't be able to recover, but he saved two other kids in the family.

But better testing——

Senator BROWNBACK. I'm sorry——

Mr. BARSH. Yes?

Senator BROWNBACK.—Mr. Barsh——

Mr. BARSH. Yes.

Senator BROWNBACK.—let me back up on this a bit. What time was it caught in him?

Mr. BARSH. He was about, I would say, seven or 8 years old, and he had been seeing physicians for about four or 5 years for some type of problem that had been misdiagnosed as everything—ADD, ADHD, Asperger's Syndrome—which is very common with our type of disease.

So I'd say I think the other thing that Congress could do would be to pass legislation, from a healthcare point of view—and I'll just talk to one narrow area, which is children. Children that display some type of mental delay, or some type of symptom that wants to be diagnosed as ADD or ADHD—a very simple, painless MRI can be performed on their brains just to make sure it's nothing else.

In certain countries in Europe today—I believe, in France—it's actually mandated. If a child has developmental delay, they do an MRI to check. That's how you could catch a lot of these diseases, because they slip through.

A typical pediatrician, our pediatrician, that has Spencer as a patient, that had ALD, she'll never see another child in her career with the disease. Around one in 10–13,000 kids has ALD. And it's so rare a single pediatrician would see it.

So I think better education for physicians, and laws mandating that children that have some type of developmental delay be

screened. Again, screening right after birth for a number of these diseases—you know, West Virginia screens for two diseases. Pennsylvania screens for about 26. It differs state by state.

Senator BROWNBACK. Can you screen before birth for ALD?

Mr. BARSH. Yes, you can. You can screen at CVS testing. You can screen during amniocentesis. It's not typically screened today, because, the genetic testing labs will tell you, "You can't screen for everything. Otherwise, we'll be screening for forever." So they do it—if there's a family history, they can absolutely screen for it today.

Senator BROWNBACK. Are there treatments, even before birth? Are there in-utero treatments?

Mr. BARSH. Not really. One of the things I believe some researchers are looking toward the future of doing in-utero cord-blood transplants, which, to me, is staggeringly interesting. But, yes, you could absolutely, if you knew.

And that technology—it's not there today, I believe. And I think Dr. Kurtzberg could address that specifically. But——

Senator BROWNBACK. Dr. Kurtzberg, would you mind sitting up here? I know this isn't the way we normally proceed. And if any of the other researchers want to pitch in, but I really would like to get at this point, about at what age and stage can cord blood can be the most successful.

Dr. KURTZBERG. Well, newborn screening could be available for most of these diseases. But it is not available on a routine basis or a mandatory basis. And even when parents request it, most of the time their pediatricians think it's not indicated. But if it was part of the standard newborn screening panels, it would be wonderful.

And what would be needed for that is, you know, an RFP to invite proposals to develop simple technology on dot-blot testing for newborn screening for these metabolic diseases.

Senator BROWNBACK. Which do not exist today.

Dr. KURTZBERG. Well, I mean, there are researchers working on the technology. It does exist, but it is not implemented in the United States, and it should be. Because all of these diseases would fare better if they were treated early in life. And regardless of what disease you're treating, children do better with transplant earlier in life. We don't have to use quite as much chemotherapy. They tolerate the procedure better.

I don't know if you remember, but our young Krabbe kids have 100 percent survival because they're healthier. And even though they have that bad disease, the rest of them can tolerate the therapy and the medicines easier.

Senator BROWNBACK. What about in-utero diagnosis and treatment?

Dr. KURTZBERG. Well, yes, there are—diagnosis is certainly possible. Parents can also be screened to see if they're carriers so they know whether or not they would be possibly conceiving a child with the disease. There's something called pre-implantation diagnosis, which allows selection of a healthy embryo. More commonly, people use CVS or amnio, as Steve mentioned, to make an in-utero diagnosis.

In-utero treatment is more complicated. There have been transplants tried in the second or third trimester. You obviously can't give a fetus chemotherapy. And most of the time they're either rejected because the fetus has enough of an immune system to not retain the cells; or there are too many cells, and the balances are off.

What probably would work and has been demonstrated in animals is that if you did the transplant in the first trimester of pregnancy, which would require diagnosis by CVS, those cells would probably be tolerated by the fetus because it's in a state called a pre-immune state. But no one knows that for sure, and a lot more research has to be done to prove that. But, theoretically, and in animals, that looks like the way to go.

Senator BROWNBACK. We're looking to set up a hearing on in-utero treatments, because there's a burgeoning field of treatments that—some spina bifida is being successfully treated in utero—that are really, really fantastic.

Dr. KURTZBERG. Well, you would a 10- to 12-week fetus and inject cord-blood cells into the belly, or the forming abdomen, and those cells would induce tolerance so that, later, they could be boosted, after birth, without chemo.

Senator BROWNBACK. Well, that's interesting.

Dr. KURTZBERG. But you have to know that the baby has the diagnosis, and that, again, has been done in animals, but not in people.

Senator BROWNBACK. This procedure you've described has not been performed on people.

Dr. KURTZBERG. No.

Senator BROWNBACK. But it has been successful in an animal model.

Dr. KURTZBERG. Correct. And there are people talking about implementing it in people. But it takes a lot of things to come together. I mean, you have to know there's a risk, someone has to have a CBS, and then you have to be able to mobilize the donor in a week, which you could do with cord blood.

Senator BROWNBACK. Mr. Sprague, in your treatment and the situation you're in, what advice do you give to patient groups? You said you speak quite a bit. Is it early screening? Do we have to do more in the cord-blood field? Is it to look at the option of cord blood, which a lot of people don't know about, instead of bone marrow?

Mr. SPRAGUE. Early detection is kind of interesting for blood cancers. There are few symptoms. Usually the diagnosis is a total shock, because you don't feel like you have cancer. You know you have a blood cancer, by a simple blood test. So one of the easiest things for everybody to do is just check your oil once in awhile. Get a blood test and make sure that everything is OK. Some of us do that religiously; some of us seldom do it.

Once you've been diagnosed with a blood cancer, while chemotherapy will only keep the disease manageable—and, in some cases, for many, many years—it's just known that the only cure—and leukemia is one of the few cancers that people can look you in the eye and tell you you're cured—is a successful stem cell transplant. The problem, as I said earlier, is if you can't find a stem cell

match, then you have no cure, and you sit home, and you wait to die.

When you compare having to go through a marrow search with the ability to find a cord-blood match sitting on the shelf somewhere—already typed, already collected, already screened, already matched to your particular type—I mean, that's going to save you months, sometimes more than months. And usually when patients decide to go to transplant, they're in the serious stages of the disease.

When you're feeling pretty good and you've been early diagnosed with the leukemia, transplant is something you think is way down the line. So if you can improve the time to find a match by having an inventory of stored cord blood, as opposed to a bunch of people who have, out of the goodness of their heart, said, "I'll be a donor if I match somebody and if you can find me when the time comes to get my marrow," that's going to save an awful lot of lives of blood cancer patients who are in distress to the point where if something doesn't happen quick, then they're going to die.

Senator BROWNBACK. Mr. Penn, you've got quite a remarkable story that you've put forward in being cured of sickle cell anemia. What's your advice to others that have suffered under the same disease that you've gone through? Is it to really seek to find cord blood that can match and that can do this and at earlier ages?

Mr. PENN. Yes. Because, I mean, I can only imagine how hard it is on other people. And I'm just one kid with sickle cell. I mean, you could walk up to anybody today, and they could have sickle cell. They probably wouldn't tell you, but—and there's probably a lot of people in the world who have sickle cell and who are looking for a cure. And this could really help them.

And if I could help them, I would like to. I mean, I'd do all I can to make sure nobody goes through what I went through.

Senator BROWNBACK. How many years ago did you go through the procedure?

Mr. PENN. Five years ago.

Senator BROWNBACK. Five years ago.

Mr. PENN. Yes, it'll be 5 years on December 11.

Senator BROWNBACK. And it was very difficult for you at that time, going through the chemotherapy and——

Mr. PENN. Yes.

Senator BROWNBACK. Now, if this had been caught earlier and tried earlier, would that have been easier?

Mr. PENN. Probably. Because your body's more healthy when you're a baby, so your body's able to accept the chemotherapy when you have to do the chemo. And since my body had aged, my body really didn't accept it that much. The cells either—since the cells had been in my body so long, they were fighting it off. That's probably why I got graft versus host disease, too.

Senator BROWNBACK. Dr. Kurtzberg, is this one that could have been—if you know and have a family history—diagnosed in utero, the procedure started that you had described?

Dr. KURTZBERG. Certainly with the appropriate research on the procedure. But most states have screening programs for sickle cell in newborns, so it is pretty universally diagnosed at birth now. And medical therapy, like antibiotics and extra visits to the pediatrician

and education of parents about crises, et cetera, is started in the first year of life. If those babies were transplanted in the first year of life, one, they would tolerate it better, they would have a higher survival. They wouldn't have damage to their tissues that sickle cell, itself, causes or the transfusions cause. So the whole process is easier. And, hearing Keone's story, how he had to miss school and how, socially, he had issues because he was sick and he couldn't attend school normally, are avoided when you transplant a newborn. Because by the time they recover, they're two or one and a half, and they're at a point where they really haven't missed out on school or other social developmental things that older children need to have.

Senator BROWNBACK. Is this being done regularly now in sickle cell diagnosis? Is the cord blood?

Dr. KURTZBERG. The diagnosis is regular. Cord blood transplant is not regular.

Senator BROWNBACK. Why not?

Dr. KURTZBERG. Because, I think, the hematology community worries about the mortality risks. And there is a natural study of sickle cell disease, which is ongoing, which shows that not all patients will have a severe course. Some do and some don't. And there have yet to be predictors identified that say which of the patients will be having strokes as children, et cetera. And so, because of that, there's been a reluctance to recommend that all children with the disease are treated.

And thalassemia, which is another hemoglobin problem where children don't make red cells effectively at all and are dependent on transfusions from the age of about five or 6 months, there's more acceptance to doing it in infancy because it's known that that disease, because if iron buildup, will be fatal in usually the second or third decade of life.

Senator BROWNBACK. Now, in Keone's case, where at age five, had a stroke, he would be clearly be somebody that you would say we need to do the cord blood, with the knowledge that we have now.

Dr. KURTZBERG. Right. Correct. And that is starting to happen. Yes.

Senator BROWNBACK. Good.

Dr. KURTZBERG. But, you know, just as a point, in some states, Medicaid won't cover HLA typing for a sickle cell patient. That's the tissue typing that you need to have to know: Do you have a donor in your family or do you need to look for an unrelated donor? So that's not even a universal health care benefit, and it certainly should be.

The other thing I wanted to say about genetic diseases is that parents are a huge resource, and they are huge advocates for their children. And as much as it's important to educate pediatricians, of which I am one, I think that the parents can be empowered, in large part, to do a lot to get their children screened and to use tests that might be made available to them. And that parental education about some of these diseases would help make things happen. And with the Internet, there's a huge tool now to bring about some programs that would be beneficial to all, and not that expensive to implement.

Senator BROWNBACK. Ms. Penn, do you have anything to tell us about your experience with this?

Ms. PENN. Well, there's quite a few things I could actually tell you. In Keone's experience, his life has been pretty difficult with sickle cell. And, like he said earlier, if there's a opportunity or a chance that another child doesn't have to go through things that my child has been through, that's a gift from God, and hopefully, this will bring about some change.

Senator BROWNBACK. Yes. Hopefully, it will.

Thank you very much. This has been a very encouraging group, all of you. You've been very thoughtful.

I hope all of you do public service announcements, get the word out. I hope there's lots of comments and quotes that are attributed to you, because I think this is the sort of thing we need to build a lot of knowledge and exposure to. This is a truly remarkable set of developments that—areas we hadn't thought we had much hope—and a whole new alternative to be able to go with.

I'm very heartened by this and by your comments. That's another area for us to look at, is the Medicaid coverage on the sickle cell blood typing.

Dr. KURTZBERG. HLA typing. Tissue typing or HLA typing.

Senator BROWNBACK. OK.

Well, thank you. God bless you all for coming forward. Thanks for being here. And hopefully we'll make some good progress in this area.

The hearing is adjourned.

[Whereupon, at 4:33 p.m., the hearing was adjourned.]

A P P E N D I X

TESTIMONY OF THE AMERICAN ACADEMY OF PHYSICIAN ASSISTANTS

On behalf of the more than 46,000 clinically practicing physician assistants in the United States, the American Academy of Physician Assistants is pleased to submit comments in response to the Subcommittee's June 12 Hearing on Advances in Adult and Non-Embryonic Stem Cell Research.

The Academy applauds the wonderful advances in adult and non-embryonic stem cell research that were highlighted in the Subcommittee's hearing of June 12. The field of regenerative medicine does indeed offer great hope to individuals who are suffering from disease. However, to fully realize the enormous potential benefits in medical research and human healing, the AAPA believes that the use of human embryonic stem cell research, including the use of nuclear transplantation techniques (also known as non-reproductive, research or therapeutic cloning), must also be fully supported. The promises of human embryonic stem cell research are, through its eventual application in the hospital and office, to ease human suffering, save lives and harness fundamentally novel avenues for patient care.

Physician Assistants (PAs)

Physician assistants are legally regulated in all states to practice medicine as delegated by and with the supervision of a physician. Physicians may delegate to PAs those medical duties that are within the physician's scope of practice and the PA's training and experience, and are allowed by law. A physician assistant provides health care services that were traditionally only performed by a physician. Forty-seven states, the District of Columbia, and Guam authorize physicians to delegate prescriptive privileges to the PAs they supervise. An estimated 170 million patient visits were made to PAs and approximately 213 million medications were prescribed or recommended by PAs in 2001.

PAs work in virtually every area of medicine and surgery and are covered providers of physician services through Medicare, Tri-Care, and most private insurance plans. Additionally, PAs are employed by the Federal Government to provide medical care, including the Department of Veterans Affairs, the Department of Defense, and the Public and Indian Health Services.

American Academy of Physician Assistants (AAPA)

The American Academy of Physician Assistants was founded in 1968 and is the only national organization representing physician assistants (PAs) in all medical specialties. The Academy educates the general public about the PA profession, assures competency of PAs through active involvement in the development of educational curricula and accreditation of PA programs, provides continuing education, and conducts PA-related research. The mission of the Academy is to promote quality, cost-effective health care, and the professional and personal growth of physician assistants.

AAPA Policy on Stem Cell Research

The AAPA's policy on stem cell research is based on the desire to promote the intense, vigorous, and responsible scientific research that will be necessary to realize the potential medical benefits of using stem cells to treat disease and repair tissue damaged by disease or trauma. The research holds tremendous promise for the development of new treatments for a wide range of serious illness and injury, such as Parkinson's disease, Alzheimer's disease, cancer, diabetes, heart disease, arthritis, neurodegenerative and immunodeficiency diseases, and spinal cord injury.

The AAPA policy on stem cell research was adopted by the Academy's House of Delegates in 2002 and 2003. Four principles are core to the Academy's collective policy—

- Federal funding must be used to support embryonic stem cell research.

- Productive research requires a larger source of stem cell lines than those in existence on August 9, 2001, necessitating the isolation of new embryonic cell lines.
- The cloning of human beings for the purpose of reproduction must be prohibited.
- The use of nuclear transplantation techniques should be promoted as a desirable means to create embryonic stem cells for research purposes.

The AAPA believes the Federal government is the single, best source for the large and sustained financial investment needed to move the research forward. The Federal government must play an important role in providing public review, approval, and monitoring of the research, as well as insuring the scientific and ethical appropriateness of the research.

Concerns regarding the age, quality, ownership, and racial and ethnic variability of the cell lines available on or before August 9, 2001 led the AAPA to support the isolation of new embryonic cell lines. Questions about whether appropriate informed consent from the donors of embryos that had been used to develop the earlier cell lines further substantiated the need to support the isolation of new embryonic cell lines.

In developing its support for embryonic stem cell research, the Academy addressed difficult ethical considerations, which led to policy being adopted to safeguard the use of donated embryos, including the appropriate use of excess, abandoned, or non-transferable frozen embryos currently stored at *in vitro* fertilization clinics.

In 2003, the AAPA affirmed and strengthened its opposition to the inappropriate use of human embryos by adopting policy to support a legally enforceable ban on the cloning of human beings for the purpose of reproduction.

The creation of stem cells by nuclear transplantation is supported as an ethically responsible means of isolating new embryonic stem cell lines, because the procedure does not involve implantation of a blastocyst in a uterus, nor is it intended to lead to the birth of a cloned human being. The stem cells that are produced are unspecialized cells that can renew themselves indefinitely and, under the right conditions, develop into more mature cells with specialized functions. Furthermore, the cells are created with the express permission of the donor and the express understanding that the tissue will be used for stem cell derivation only, not for implantation and reproduction.

The AAPA believes that stem cell research and nuclear transplantation hold tremendous potential to ease human suffering through advanced therapies. The Academy applauds the Subcommittee's use of the June 12 hearing to showcase the remarkable advances in medicine that have been made in the fields of adult and non-embryonic stem cell research. However, the Academy also urges the Subcommittee to consider the appropriate and responsible use of embryonic stem cell research. No other current avenue of medical research holds the promise of human embryonic stem cells.

Thank you for the opportunity to submit the comments of the American Academy of Physician Assistants to the Hearing Record.

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